The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 2 FEBRUARY, 1942 NUMBER 2

Simmonds' Disease

A Clinical Study with Review of the Literature; Differentiation from Anorexia Nervosa by Statistical Analysis of 595 Cases, 101 of Which Were Proved Pathologically[1]

[Hypophyseal Cachexia]

ROBERTO F. ESCAMILLA, M.D.
AND H. LISSER, M.D.

From the Department of Medicine, University of California Medical School, San Francisco, California

THE HISTORICAL SEQUENCE in the development of knowledge concerning a disease usually follows a fairly constant pattern. First an author of exceptional discernment reports one or several cases with a group of symptoms or pathological findings which in his opinion justify the postulation of a new syndrome. Subsequent authors add similar cases and further observations, and, as the general experience widens, more complete and precise information concerning the disease is accumulated. In the course of time the suggestion is made that the original author's name be used in designating the disease. Such tribute to an original concept seems altogether fitting and at the same time furnishes a historical perspective. Diverse opinions concerning the necessary criteria for diagnosis are expressed. Therefore a periodic critical review of the accumulated knowledge is of considerable value in clarifying and appraising these varying points of view.

Thus, it was Morris Simmonds (1855–1925) (1), pathologist of the University of Hamburg, who in 1914 first suggested that the clinical syndrome now known as hypophyseal cachexia was due to severe pathologic interference with the function of the adenohypophysis. The diagnosis in the original report was based upon findings at autopsy. Four years later Nonne of Hamburg (reported by Bostroem, 2) made the first diagnosis in a living patient; this diagnosis was later verified pathologically and reported by both Simmonds (3, 4) and Bostroem (5).[2] The first proved case in which attention was called to a low basal metabolic rate was that of Monakow (7) in 1922. During the same year Lichtwitz (8) first used the designation

Received for publication August 26, 1941.
[1] Aided by a grant from the Christine Breon Fund for Medical Research.
Presented in summary before the Annual Meeting of the Association for the Study of Internal Secretions, San Francisco, June, 1938.

[2] Leschke (6) claimed the distinction of being the first to diagnose hypophyseal cachexia during life.

'Simmonds' disease' in the title of his publication.

Since then, many cases have been reported in the literature and varying views have been expressed concerning the syndrome. This diversity is due in part to the fact that quite typical cases are seen occasionally without pathological changes in the pituitary body. The reverse is also true, namely, destruction of the pituitary may be complete without the usual clinical picture of hypophyseal cachexia; for instance, obesity rather than emaciation may occur. Further confusion is caused by the observation that in rare instances a case of Addison's disease may simulate Simmonds' disease. However, the greatest confusion is brought about by the disturbing experience that true anorexia nervosa, originally described by Gull in 1868, may simulate hypophyseal cachexia in every important detail.

These perplexities have led to many errors in diagnosis so that the time seems ripe for a comprehensive review and an analysis of the available facts concerning the disease. This purpose would seem to be accomplished best by a critical study of the details of previously reported cases. Therefore, the literature has been surveyed as completely as possible up to January 1940 and a few cases have been added after this date.[3] With rare exceptions, each article has been consulted in the original publication in an attempt to eliminate the repetition of errors made in previous comprehensive summaries, and the consideration of the same case more than once.

Synonyms

It will be recalled that when Cushing published his first article on 'pituitary basophilism,' he included cases from the earlier literature published under other designations which he regarded as characteristic examples of the new syndrome. We have likewise included in our analyses several cases published prior to 1914, such as the one of Ponfick, 1899 (9), which seem to us characteristic of Simmonds' disease. Extremely interesting in this connection is Sheehan's discovery of a group of cases reported in 1883 by Simpson (10) under the title, "Superinvolution of the uterus." Simpson found an incidence of 22 in 1300 patients (1.7%) with an average age of 30, many of whom had amenorrhea and 'wasting' which seemed to date from marked loss of blood at parturition. The data were not sufficiently detailed to warrant inclusion in our analysis, but it is altogether likely that some of these were instances of true pituitary cachexia.[4]

In all likelihood the cases reported under the two designations, 'insuffisance pluriglandulaire' by Claude and Gougerot in 1907–1908 (14, 15, 16,), and 'multiple ductless glandular sclerosis' by Falta (17, 18, 19) should really have been classified with Simmonds' disease and consequently are incluced in our data. At that time (early twentieth century) little was known of the manner in which the anterior pituitary, now frequently referred to as the 'master gland,' dominates the hormonopoietic system. Hirsch and Berberich (20), were the first to suggest that cases previously reported as 'pluriglandular insufficiency' might be instances of true Simmonds' disease. In 1928 Thür (21) suggested that Simmonds' disease and multiple glandular sclerosis were similar and might be related, and in 1938 Herrick (22) and Meyler (23) expressed the opinion that the two conditions were identical. The designation, 'pluriglandular insufficiency,' has also been used by Petschacher and Hönlinger (24), Zondek (25), Stenström (26), Usadel (27), Wachstein (28), and Lindemann (29). 'Multiple ductless glandular sclerosis' has been used after Falta by the following authors: Hochstetter (30), Lindemann (31), Kiyono (33), Dimmel (34), Lisser (35), Richter (36), Bingold (37), Liebers (38), Heinrichs (39), Umber (40), Rössle (41), Boller and Goedel (42), Dunn (43), Oyamada and Otomo (44), Meerwein (45), and Priesel (46). What is known as progeria may be Simmonds' disease as it appears in younger people with emphasis on the symptom of premature senility; Rand in 1914 (47) suggested that pituitary disturbance may be chiefly responsible for this clinical syndrome.

Furthermore, certain cases that we regarded as sufficiently characteristic to include in our analysis were published under the following designations: 'Myxedema with testicular atrophy' (48); 'Myxedema or cretinism with pituitary changes' (9, 49, 50, 23, 51); 'Non-operative myxedema' (52); 'Operative myxedema' (53) (following removal of two hypertrophied breasts in a male); 'Acquired myxedema with sexual regression,' (54); 'Infantilisme reversif,' (55); 'Insuffisance endocrinienne thyroide-testiculaire,' (56); 'Encocrine cachexia,' (57); 'Infantilisme tardif de l'adult,' (58, 59); 'Insuffisance pluriglandulaire interna thyro-testiculo-surrénale,' (60); 'Insuffisance diastémato spermatique acquise avec atrophy thy-

[3] Although the local library facilities, including the University of California Medical Library, the Lane Medical Library, and the Library of the San Francisco County Medical Society are extensive, some of the smaller foreign journals are not available. A few articles of particular interest were obtained through the mailing services of the New York Academy of Medicine and the Surgeon General's Library.

[4] Hun and Prudden (11) reported the case of a woman aged 54 who had mental derangement, terminal anorexia, diarrhea and emaciation; at autopsy atrophic fibrosis of the thyroid was found. The case was reported as 'Myxoedema.' Pituitary endocrinopathies were not known at that time and the atrophic fibrosis of the thyroid may well have been secondary to pituitary disease. There are many other cases in the older literature with clinical narratives suggestive of Simmonds' disease in which the end was fatal but the pituitary was not examined. Some of these were labelled anorexia nervosa because the authors were aware of this disease as described by Gull in 1868 (12, 13).

roidienne,' (61); 'Polyglandular, multiglandular or (pluriglandular syndrome or disease,' (62–69); 'Myxedema,' (17, 70); 'Preadolescent hypopituitarism; posterior lobe insufficiency without anterior lobe involvement,' (71); 'Addison's disease with pluriglandular disturbance,' (72); 'Dystrophia cachectogenitalis,' (73, 74); 'Presenile involution,' (25); 'Senium praecox' (25); 'Thyrosexual insufficiency,' (75); 'Luetic cachexia,' (76); 'Spontaneous hypoglycemic coma,' (77); 'Cerebral Magersucht (thinness),' (78–81); 'Zerebral-hypophysaere Magersucht,' (82, 83); 'Magersucht (thinness)' (84–86,[5] 88–95, 29); 'Post-partual Magersucht,' (96); 'Hypophyseal Magersucht or Maigreur,"(97–102); 'Hypopituitarismus totalis,' (103); 'Asthenia gravis hypophyseogenea,' (104); 'Interreno-insuläre Syndrom,' (105); 'Primäre Polynesie,' (105, 106); 'Hypophyseothyrogenic emaciation,' (107); 'Hypophyseal thyrogenital syndrome,' (108); 'Late pubertal emaciation,' (109, 110, 111); 'Post partum emaciation,' (112); 'Nonmyxedematous hypothyroidism,' (113); 'Hypopituitarism,' (114, 115).

The term, 'cachexia hypophyseopriva,' was first suggested by Elsberg and Krug in 1917 (116) and has been used frequently since then.

Reviews

The most important collections of reported cases of Simmonds' disease were compiled by Leschke, 1919 (6), 21 cases;[6] Graubner, 1925 (117), 34 cases; Tauber, 1927 (118), 10 cases (summarized in tabular form); Calder, 1932 (119), 70 cases; Silver, 1933 (120), 41 accepted cases; Howard and Rhea, 1936 (121), 71 cases; Robert, 1936 (122), 90 cases (with details presented in tabular form); and Van Balen, 1939 (123), 82 cases (of which the author accepts 22 as Simmonds' disease). Sheehan, 1939 (124), has tabulated a special group confined to cases of Simmonds' disease consequent to postpartum necrosis of the anterior pituitary. He analyzed 32 cases which were verified at autopsy and 19 cases which were typical clinically.

CLASSIFICATION OF CASES

In 1938 we (125) presented the observations made in eight cases which were considered typical clinical examples of Simmonds' disease. Of these, two patients had died and the clinical diagnosis of one was verified at autopsy. Subsequently (126) we published a short summary of a critical statistical study comprising 69 cases verified at autopsy and 134 typical clinical cases; most of the patients in the latter group were alive and in those who had died no pathological investigations had been made. In the present paper, the factual data upon which the previous one was based are considered far more comprehensively. Several new case records of patients seen by us personally have been added (see *Case Summaries* at the end of this paper), and in addition the details concerning certain unpublished cases seen by other physicians have been made available to us. Necessary additions to and rearrangements and reclassifications of cases account for any discrepancies which may have occurred in figures or percentages. Furthermore, we have considered in this paper, cases which we regard as suggestive rather than convincing examples of Simmonds' disease. For purposes of classification and comparison the eight groupings given below have been made. Under each group are listed bibliographic references to the literature on these cases. Within each set of parentheses are cited all of the references to an individual case. It will be noted that some cases have been reported more than once, by the same or by different authors. The references in each group are listed in chronological order.*

Group A. Typical Clinical Cases, with Pathological Verification

The 101 cases we have included in this group are those reported as follows: (9), (14, 15), (56, 60), (17, 133), (63), (1, *case 1;* 134, *case 12;* 4, *case 1*), (135, 64), (136, *case 1;* 137 *case 1*), (136, *case 2;* 137, *case 2*), (138), (139, 140, 4, *case 2*), (2, 5, 141, 3, 4, *case 3*), (4, *case 4*), (6), (142), (143, 144, *case 1;* 145 *case 2*), (146, 7), (147, *case 8*), (148, 30), (149, 150, 151, 152, *case 1*), (153) (154, *case 24*), (155, *case 1;* 65, *case 1*), (156, 25, *case 4;* 157, 158, *case 2*), (159, 25, *case 2;* 157, 33, *case Vb;* 148, *case 10*), (160), (161), (162), (25, *case 5;* 157, *case 6;* 158, *case 6*), (163, *case 1*), (164, *case 1;* 165, *case 2;* 166), (164, *case 2;* 165, *case 1*), (167), (20), (117), (168, 169), (34), (170), (171), (172, *case 1*), (77), (173), (174, *case 7*), (175), (21), (176, *case 1*), (177), (36), (178, *case 1*), (179), (180), (181), (182, *case 1;* 183, *case 2*), (182, *case 2;* 183, *case 1*), (182, *case 3;* 183, *case 4*), (184, *case 1;* 185, *case 2*), (186), (187), (188, *case 2*), (39), (189, *case 1*[7]), (190), (191, *case 3*), (185, *case 1;* 86, *case 4*),

[5] Subsequently von Bergmann (87) altered his conception of allying the group of cases he had called 'Magersucht' to hypophyseal cachexia and considered them to be of psychogenic origin.

[6] All but two of the cases referred to by Leschke have been read in the original publications. Only 6 of these could be regarded as instances of Simmonds' disease and have been included in our analysis of verified cases (*group A*). It is only fair to state that Leschke's elaborate article was concerned primarily with pathological lesions involving the hypophysis or hypothalamus and their relation to diabetes insipidus. The 21 cases referred to include 3 of total destruction of the anterior lobe only and 18 of destruction of the entire pituitary body.

* Extensive tables have been prepared, listing the cases in each of these groups and summarizing the following data for each case: sex; age; weight-loss; asthenia; duration of amenorrhea; frigidity or loss of libido and potency; psychic changes; anorexia; cachexia or emaciation; amount under ideal weight; premature senility; loss or absence of axillary or pubic hair; genital atrophy or infantilism; blood pressure; B.M.R.; blood sugar and sugar tolerance; results of treatment; and miscellaneous.

For these detailed tables order Document 1604 from *American Documentation Institute, Offices of Science Service, 2101 Constitution Avenue, Washington, D. C.* remitting 75 cents for microfilm form.

[7] This case presents a Simmonds'-like picture resulting from a destructive lesion of the pituitary body. Some may be inclined to question the diagnosis of Simmonds' disease and call it pituitary dwarfism with infantilism (and it was so regarded by Cushing). However, hypophyseal infantilism when produced by a suprasellar cyst or chromophobe adenoma is not as a rule associated with loss of weight and a very low basal metabolic rate. The presence of these two factors influences us to include this case as one of Simmonds' disease.

(192), (41, *case 3*), (193, 194, *case 2*), (195), (132, *case 11*; 196, *case 2*; 197, *case 3*; 198, *case 3*), (42, *case 1*), (42, *case 2*), (69), (199), (200), (121), (201, 202), (109, *case 1*; 198, *case 22*; 110, *case 1*; 111, *case 11*), (109, *case 2*; 198, *case 17*; 110, *case 3*; 111, *case 10*), (203), (204), (205, *case 1*), (206), (45), (207), (125, *case 2*; 126, *case 1*), (208, *case 1*), (208, *case 2*), (209), (210, *case 1*), (210, *case 2*), (211), (212), (114, *case 1*; 115, *case 1*), (114, *case 2*), (114, *case 3*), (213), (214), (215), (216), (217), (present report, *case 1*).

Group B. Typical Clinical Cases, without Pathological Investigation

The 158 cases included in this group are those reported as follows: (57, *case 1*), (61), (116), (71), (218, 219), (147, *case 1*), (220, 221), (8, *case 27*; 222, 223, 224), (154, *case 23*), (18), (25, *case 1*; 157, *case 9*; 158, *case 9*), (73, *case 1*; 157, *case 7*; 158, *case 7*), (73, *case 2*; 157, *case 8*; 158, *case 8*), (157, *case 4*; 83, *case 1*, 158, *case 4*), (157, *case 5*; 83, *case 3*; 158, *case 5*), (225), (226), (227, *case 3*), (228, *case 1*), (228, *case 3*), (228, *case 4*), (229, 230), (231), (68), (232, *case 1*), (232, *case 2*), (233), (234), (235), (236, *case 1*), (237, 132, *case 1*; 198, *case 20*), (37), (238), (239, *case 7*; 240, *case 6*), (241), (242), (243, 132, *case 2*), (244, *case 1*), (244, *case 2*), (244, *case 3*), (188, *case 1*), (188, *case 3*), (83, *case 2*), (245), (246), (247, 132, *case 3*; 109, *case 14*; 110, *case 13*), (248), (191, *case 1*), (249), (85, *case 2*; 86, *case 14*), (86, *case 1*; 112, *case 2*), (86, *case 2*; 112, *case 3*), (86, *case 3*; 112, *case 4*), (86, *case 5*; 112, *case 5*), (86, *case 6*), (86, *case 7*), (86, *case 8*), (86, *case 9*), (86, *case 12*), (86, *case 15*), (250), (251, 252), (253), (254, *case 5*), (255, *case 2*; 256, *case 2*; 257, *case 2*), (255, *case 3*; 256, *case 3*; 257, *case 3*), (132, *case 8*), (132, *case 9*; 196, *case 1*; 197, *case 2*; 109, *case 10*; 198, *case 1*; 110, *case 11*; 111, *case 1*), (132, *case 10*; 258 *case 1*; 197, *case 4*; 109, *case 12*; 198, *case 5*; 110, *case 12*; 111, *case 2*), (259, *case 1*), (259, *case 2*), (98, *case 1*), (260, *case 3*), (260, *case 4*), (261, 262, *case 1* ?), (99, 112, *case 7*), (104, *case 1*), (104, *case 2*), (104, *case 3*), (263), (264), (265), (266), (267, *case 3*; 258, *case 6*; 197, *case 7*; 109, *case 13*; 198, *case 7*; 110, *case 9*; 111, *case 4*), (267, *case 5*; 258, *case 9*; 197, *case 10*; 198, *case 9*), (268), (269, *case 1*), (270), (107), (197, *case 6*; 109, *case 4*; 198, *case 6*; 110, *case 5*; 111, *case 3*), (197, *case 8*; 271, *case 10*; 109, *case 6*; 198, *case 10*; 110, *case 7*; 111, *case 5*), (197, *case 12*; 271, *case 13*; 109, *case 9*; 198, *case 14*; 110, *case 14*; 111, *case 6*), (197, *case 14*; 271, *case 11*; 109, *case 7*; 198, *case 12*; 110, *case 8*; 111, *case 7*), (109, *case 11*; 198, *case 21*; 111, *case 12*), (272), (112, *case 8*), (198, *case 18*; 110, *case 2*; 111, *case 13*), (273), (274), (275), (276, *case 1*), (276, *case 2*), (276, *case 3*), (127, *case 1*), (127, *case 3*), (127, *case 5*), (127, *case 6*), (127, *case 9*), (127, *case 10*), (277, *case 1*), (277, *case 2*), (277, *case 3*), (278), (279), (240, *case 7*), (280, *case 1*), (100, *case 1*), (100, *case 4*), (100, *case 5*), (281), (282, *case 1*), (101), (125, *case 1*), (125, *case 4*), (125, *case 6*), (125, *case 8*), (125, *case 9*), (23, *case 1*), (23, *case 2*), (23, *case 3*), (23, *case 4*), (23, *case 5*), (23, *case 9*), (23, *case 11*), (283), (284), (285, *case 1*), (286, *case 1*), (286, *case 2*), (287, *case 3*), (287, *case 4*), (288, *case 1*), (288, *case 2*), (289, *case 2*; 290, *case 2*), (291), (292, *case 2*), (293), (114, *case 6*), (114, *case 7*), (115, *case 7*), (294, *case 9*), (295, *case 1*), (295, *case 2*), (296), (297), (298), (present report, *case 2*), (present report, *case 3*).

Group C. Suggestive Cases Lacking One or More of the Cardinal Clinical Findings; Some with Pathological Findings

The 180 cases included in this group are those reported as follows: (299, *case 4*), (52), (53), (54, *case 1*), (49), (17, *Obs. XII*; 133, *Obs. XII*), (47, 227, *case 2*), (300, *case 1*), (301, *case 1*; 302), (303, 304 305), (306, 307), (308), (309, 310) (311, *case 2*; 35), (72), (312, *case 10*), (154, *case 25*), (8, *case 2*), (8, *case 3*), (31), (75, *case 1*), (313), (314, *case 2*), (76, *case 1*), (157, *case 3*; 158, *case 3*), (315, *case 2*), (315, *case 19*), (144, *case 2*), (144, *case 3*), (26), (66), (227, *case 1*), (228, *case 5*), (316), (317, *case 2*), (82, *case 1*), (82, *case 2*), (82, *case 3*), (318, 319), (84, *case 4*), (320), (321, *case 3a*), (96, *case 2*), (322), (323, 324, *case 1*), (178, *case 2*), (325), (324, *case 2*), (324, *case 3*), (324, *case 4*). (326), (236, *case 3*), (184, *case 2*), (184, *case 3*), (38), (327), (83, *case 4*), (97), (120), (328), (329), (330), (27, *case 1*), (191, *case 2*; 260, *case 2*), (331, *case 4*; 132, *case 4*), (331, *case 5*; 132, *case 5*), (331, *case 6*; 132, *case 6*), (331, *case 8*), (332), (333), (40, *case 3*), (86, *case 10*), (86, *case 11*), (86, *case 13*), (103), (334), (335), (255, *case 1*; 256, *case 1*; 257, *case 1*), (28, *case 2*), (336), (132, *case 7*), (132, *case 12*; 197; *case 1*; 198, *case 2*), (337), (98, *case 2*), (98, *case 3*), (338), (260, *case 1*), (339), (90, *case 3*), (91), (340, 122), (267, *case 1*), (267, *case 2*; 197, *case 9*), (341), (43, 342), (258, *case 5*; 197, *case 5*; 198, *case 4*), (343, *case 1*), (343, *case 2*), (44), (197, *case 13*; 271, *case 12*; 109, *case 8*; 198, *case 13*; 110, *case 10*; 111, *case 8*), (344), (345), (109, *case 3*; 198, *case 19*; 110, *case 4*; 111, *case 9*), (109, *case 5*; 198, *case 23*; 110 *case 6*; 111, *case 14*), (112, *case 6*), (346, *case 1*), (346, *case 12*; 347, *case 3*), (348), (198, *case 8*), (198, *case 16*), (198, *case 24*; 111 *case 15*), (276, *case 4*), (127, *case 2*), (127, *case 4*), (127, *case 7*), (127, *case 8*), (349), (277, *case 4*), (350, *case 3*), (350, *case 4*), (350, *case 5*), (351, *case 2*), (351, *case 1*; 352, *case 1*), (352, *case 2*), (352, *case 3*), (240, *case 9*), (205, *case 2*), (353, *case 1*), (353 *case 2*), (100, *case 2*), (280, *case 2*), (29, *case 2*), (23, *case 6*), (23, *case 7*), (23, *case 8*), (23, *case 10*), (23, *case 12*), (23, *case 13*), (102, *case 1*), (102, *case 2*), (287, *case 5*; 290), (287, *case 8*), (354, discussion) (95, *case 1*), (95, *case 2*), (95, *case 6*), (95, *case 10*), (46), (289, *case 1*), (289, *case 4*; 290, *case 4*), (289, *case 7*), (355), (113), (356), (298, *case 2*), (357, *case 1*), (357, *case 2*), (357, *case 3*), (51), (292, *case 1*), (292, *case 3*), (292, *case 5*), (358), (359, *case 1*), (114, *case 4*; 115, *case 2*), (360), (361, *case 12*), (361, *case 28*), (361, *case 31*), (361, *case 34*), (361, *case 35*), (362), (363), (364, *case 29*), (115, *case 3*), (115, *case 4*), (365), present report (*case 4*), (*case 5*), (*case 6*).

Group D. Cases in Which the Diagnosis Seems Doubtful

The 43 cases in this group are those reported as follows: (48), (55), (62), (366), (50), (32), (314, *case 1*), (367), (368), (369), (370), (82, *case 4*), (371, *case 5*), (236, *case 2*), (372), (331, *case 7*), (373), (374), (375), (376), (267, *case 4*), (108), (94, *case 1*), (197, *case 11*; 198, *case 11*), (197, *case 15*), (377, *case 2*), (346, *case 3*), (346, *case 4*), (346, *case 8*), (347, *case 4*), (352, *case 4*), (378), (240, *case 8*), (353, *case 3*), (29, *case 1*), (29, *case 3*), (125, *case 5*), (125, *case 7*), (287, *case 6*), (95, *case 3*), (289, *case 8*), (292, *case 4*), (379).

Group E. Cases Showing Destructive Lesions of the Pituitary Body, but without the Typical Clinical Findings

The following 15 cases are included in this group: (380, *case 2*), (299, *case 3*), (381), (382), (70), (383, *case 6*), (384), (385), (118), (172, *case 2*), (145, *case 1*), (386, *case 12*), (387, *case 1*), (387, *case 9*), (183, *case 3*).

Group F. Typical Clinical Cases, but with Normal Pituitaries

There are 14 reported cases in this category: (388), (24), (155, *case 2*), (150, *case 2; 151, case 2;* 152, *case 2*), (389), (390), (78; 79, *II*), (80), (391), (105, 106), (392), (130), (393), (present report, *case 7*).

Group G. Cases Reported without Sufficient Data for Classification

There are 84 cases reported that could not be classified because of insufficient data: (394), (299, *case 1*), (299, *case 2*), (57, *case 2*), (395), (396, *case 1*), (397, *case 6*), (397, *case 7*), (397, *case 8*), (398), (74, *case 16*), (74, *case 17*), (25, *case 6*), (399), (163, *case 2*), (400, *case 1*), (400, *case 2*), (401), (402), (315, *case 4*), (315, *case 28*), (403, *case 4*), (67), (404, *case 1; 405, case 2*), (404, *case 2; 405, case 6*), (404, *case 3; 405, case 8*), (405, *case 1*), (405, *case 3*), (405, *case 4*), (405, *case 5*), (405, *case 7*), (405, *case 9*), (405, *case 10*), (405, *case 11*), (405, *case 12*), (405, *case 13*), (405, *case 14*), (405, *case 15*), (324, *case 5; 406, case 1*), (407),[8] (85, *case 3*), (86, *case A; 88*), (40, *case 1*), (40, *case 2*), (408), (41, *case 2*), (42, *case 4*), (81), (409), (410), (94, *case 2*), (112, *case 1*), (112, *case 9*), (112, *case 10*), (100, *case 3*), (262, *case 2*), (111, *case 16*), (111, *case 17*), (111, *case 18*), (111, *case 19*), (111, *case 20*), (111, *case 21*), (111, *case 22*), (111, *case 23*), (111, *case 24*), (111, *case 25*), (111, *case 26*), (111, *case 27*), (111, *case 28*), (111, *case 29*), (111, *case 30*), (111, *case 31*), (111, *case 32*), (287, *case 7*), (95, *case 4*), (95, *case 5*), (95, *case 7*), (95, *case 8*), (95, *case 9*), (95, *case 11*), (95, *case 12*), (95, *case 13*), (95, *case 14*), (411).

Group H. Typical Cases of Anorexia Nervosa

For puposes of comparison, 20 cases of anorexia nervosa are referred to: (125, *case 3;* 126, *case 2*), (412, *case 1*), (412, *case 2*), (412, *case 3*), (412, *case 4*), (412, *case 5*), (412, *case 6*), (412, *case 7*), (412, *case 8*), (413, *case 1*), (413, *case 2*), (414, *case 1*), (129, *case 1*), (129, *case 2*), (129, *case 3*), (129, *case 4*), (129, *case 5*), (129, *case 6*), present report (*case 8*), (*case 9*).

In order to warrant inclusion in *group A* or *group B*, the four cardinal characteristics of Simmonds' disease had to be found in the data on a given case. These characteristics are *a*), loss of weight, *b*), loss of sexual function, *c*), asthenia, and *d*), a very low basal metabolic rate (below −20%). Since the earlier cases were reported before basal metabolic rate determinations were customary, we have included them in *groups A* and *B* if they were typical clinically; furthermore, a few of the later cases in which basal metabolic rates were not reported have been admitted because in all other respects they were apparently characteristic.

A few typical cases of anorexia nervosa have been listed and analyzed in order to emphasize the striking similarity of symptoms, physical stigmata and laboratory abnormalities. This parallelism has been noted also by others, for example, by Greene (127) and Richardson (128,129) and its recognition is essential to any sound understanding of the problems involved in differential diagnosis because the two conditions may be alike in almost every detail, even in death. The final proof of the presence of Simmonds' disease rests on discovery of a destructive lesion of the adenohypophysis at autopsy. However, this criterion makes it difficult to account for the classical clinical picture (despite voracious appetite) in the patient described by Osgood (130), in whom a normal hypophysis was found at autopsy.

It is our intention to review in a subsequent paper the actual pathological lesions of the hypophysis reported in cases of true Simmonds' disease. The final paper in this series will be devoted to an analysis of the various therapeutic procedures which have been utilized, together with an appraisal of the results.

For obvious reasons, *groups D, E, F* and *G* have been excluded from the statistical analysis which follows. It would jeopardize the value of the statistics to include data from the dubious cases of *group D;* similarly, the cases in *group E* were not characteristic clinically although pathological pituitaries were found. To avoid controversy, we omitted the cases which were typical clinically but in which the pituitary body was normal. The question at once arises whether or not derangements of endocrine function are to be excluded purely because the pathologist can detect no cytological alterations. It has long been recognized that in unquestionable diabetes mellitus little or no change may be detected in the islets of Langerhans. Chemical hormonal changes may conceivably be operative in the absence of cellular abnormalities demonstrable by present methods of staining. *Group G*, in which the data are fragmentary, was automatically debarred. Although these cases were rejected from the statistical studies, they appear in this paper in order to complete the bibliography of Simmonds' disease.

Since variation in clinical findings is common to all diseases, our prerequisites for inclusion in *group A* may be too strict. Some of the cases in *group C* or even in *group E*, particularly those in which destructive lesions of the pituitary have been found, may be

[8] We have been unable to find any record of this case except in Oppenheimer's discussion of the paper of Farquharson and Graham (182). The remark that the case showed "most of the findings reviewed by Doctor Graham" leads us to believe that it probably belongs in *Group B*, but we cannot include it because of inadequate data.

TABLE 1. SEX DISTRIBUTION

Group	Number of cases	Female	Male	Ratio female: male
A (typical clinically, pathologically verified)	101 (sex not given in 1)	65 (64%)	35 (35%)	7:4
B (typical clinically, no pathologic investigation)	158	128 (81%)	30 (19%)	4:1
C (suggestive cases)	180 (sex not given in 9)	131 (73%)	40 (22%)	3:1
H (cases of anorexia nervosa)	20	18 (90%)	2 (10%)	9:1

cases of true Simmonds' disease. However, we believe that even by these stringent standards a certain percentage of the cases in *group B* actually may be instances of anorexia nervosa. Richardson (129) has so designated several of them.[9] Therefore, for purposes of comparison, we have considered it desirable and more accurate to apply the same clinical standards to *group A* and *group B*.

STATISTICAL ANALYSIS OF CERTAIN SPECIAL FEATURES

Anamnesis

Sex distribution. (*Table 1*). It is apparent at once that females predominate in all of the groups. The fact that in females anorexia nervosa is far more prevalent (9:1) than verified Simmonds' disease (7:4) seems significant. Therefore the greater frequency of occurrence in females of the unverified *group B* suggests that some of these cases may actually have been instances of anorexia nervosa, even though they appeared clinically typical of Simmonds' disease.

Age. (*Table 2*). Irrespective of what group is considered, true Simmonds' disease, or what may have been mistaken for Simmonds' disease, occurs but rarely before 10 years or after 65 years of age. It is therefore primarily a disease of adult life.

It is pertinent to observe that about half of the cases in which autopsies were made were reported prior to 1930, while less than 20 per cent of those in which no autopsies were reported were published before that time. These observations must be taken into account in appraising the age incidence in the two groups.

Most of the patients in the verified group were first seen when they were between the ages of 20 and 60 years, the mean age being 41. The corresponding figures for *group B* show predominance between the ages of 10 and 40 years with a mean age of 27. All of the instances of anorexia nervosa mentioned in this paper occurred between 13 and 35 years of age. Again, age grouping raises the suspicion that some of the cases in *group B* were instances of anorexia nervosa rather than of true Simmonds' disease.

TABLE 2. AGE DISTRIBUTION

Group	Years							
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79
A (101 typical, verified cases)	1	8	20	14	22	22	12	
B (158 typical cases, not verified)	2	56	47	26	13	9	3	
C (180 suggestive cases)	2	19	44	48	34	22	4	1
H (20 cases of anorexia nervosa)		11	7	2				

TABLE 3. WEIGHT LOSS

Group	Cases with weight loss mentioned	Cases with note of amount lost	Amount of actual weight loss		
			Maximum	Minimum	Average
A (101 typical, verified cases)	63 (62%)	42 (42%)	51 kg. (112 lb.)	3.5 kg. 8 (lb.)	20.4 kg. (45 lb.)
B (158 typical cases, not verified)	139 (90%)	104 (66%)	48.7 kg. (106 lb.)	4.5 kg. (10 lb.)	19.3 kg. (42 lb.)
C (180 suggestive cases)	109 (61%)	83 (46%)	75.5 kg. (166 lb.)	1.4 kg. (3 lb.)	16.9 kg. (37 lb.)
H (20 cases of anorexia nervosa)	14 (70%)	13 (65%)	37.7 kg. (83 lb.)	7.3 kg. (16 lb.)	19.5 kg. (43 lb.)

Weight loss. (*Table 3*). In at least 61 per cent of the cases in *groups A, B, C,* and *H*, loss of weight was specifically mentioned. However, it must have occurred more frequently in the verified group because cachexia was specifically mentioned in 65 per cent of the case reports. All of the patients included in *groups A* and *B* had some indication of weight-loss or cachexia.

The average amount of loss of weight was about the same in *groups A, B,* and *H*, namely approximately 20 kg. (44 lb.). The less typical cases of *group C* showed a slightly smaller average loss. Upon further analysis of the comparative weight-loss of males and females (which does not appear in the table), no appreciable difference was noted. The severest loss of weight suffered by any patient in *group A, B,* or *C*

[9] Sheldon (131) insisted that "large numbers of cases (of anorexia nervosa) were described, and are still being described, in all good faith as instances of Simmonds' disease. In fact, there are over 80 instances of this mis-reporting and approximately half of the published cases of anorexia nervosa are indexed under other names." An "industrious example" (of authors who make this error) was Kylin, who "in 1935 wrote a monograph on Simmonds' disease (132) which will always be one of the more important papers on anorexia nervosa."

was over 106 lb., with the highest figure (166 lb.) in *group C*. In comparison, the greatest loss in the admittedly psychotic group did not exceed 83 lb.

Asthenia. (*Table 4*). This symptom was conspicuous in all groups, but was particularly striking in the patients who eventually died (*group A*, 90%). It was shared equally by both sexes. The high percentage of incidence in the verified cases would seem to require inclusion of this symptom as one of the characteristic features of the disease; however its frequent occurrence in other maladies, notably in Addison's disease, and the fact that it may develop late in the course of true Simmonds' disease diminish its value in differential diagnosis.

Asthenia may be considered an inevitable consequence of marked loss of weight, but Meyer (95) has pointed out that this is not always true. It is well known that many thin, wiry, healthy individuals exhibit the antithesis of asthenia, namely exceptional energy and endurance.

TABLE 4. FREQUENCY OF ASTHENIA

Group	Males	Females	Total
A (101 typical, verified cases)	33 (94%)	57 (88%)	91 (90%)
B (158 typical cases, unverified)	25 (83%)	87 (68%)	112 (71%)
C (180 suggestive cases)	27 (68%)	92 (70%)	122 (68%)
H (20 cases of anorexia nervosa)	1 (50%)	10 (56%)	11 (55%)

Amenorrhea. (*Table 5*). The patients excluded in the second column of table 5 were under 11 years of age when first seen or had passed the menopause before the onset of the disease. Patients whose menstruation was scanty or irregular were not included in the third column; however, such symptoms should not be dismissed without clinical appraisal. A few females were included who were 15 years of age or over but had never menstruated.

A review of table 5 forces the conclusion that amenorrhea of longer or shorter duration is an outstanding phenomenon in groups *A*, *B*, and *H*, and a lesser but by no means negligible one in *group C* (64%). Anticipating a later analysis of the duration of symptoms, we merely note here that amenorrhea is an early symptom of either Simmonds' disease or anorexia nervosa.[10] Interestingly enough, Cushing and Davidoff stressed the fact that amenorrhea is one of the earliest symptoms in female acromegalics, and acromegaly is a pituitary endocrinopathy which is considered by some to be the opposite of Simmonds' disease.

TABLE 5. FREQUENCY OF AMENORRHEA

Group (Females)	Cases omitted because of age	Cases in which amenorrhea was specifically mentioned
A (65 typical, verified cases)	10 (15%)	45 (82%)
B (128 typical cases, unverified)	8 (6%)	117 (98%)
C (131 suggestive cases)	4 (3%)	81 (64%)
H (16 cases of anorexia nervosa)	0	18 (100%)

Loss of libido and potence. (*Table 6*). Here again, a certain number of males who were either too old or too young for the manifestation of this symptom was deducted from the totals.

Loss of libido and potency was a complaint in over half of the male patients, irrespective of whether they were classified in *group A*, *B* or *C*. This symptom may be ascribed to a deficiency of the anterior pituitary gonadotropic hormone rather than to malnutrition, since conspicuous venery has often been noted in advanced tuberculosis. Statistics were not computed in females since they rarely volunteer such a complaint and often no inquiry is made regarding it.

Psychic changes. A close parallel is observed in the incidence of psychic disturbances in *groups A*, *B* and *C* (64, 55 and 49% respectively). The presence, therefore, of mental-emotional abnormalities does not necessarily favor the diagnosis of anorexia nervosa. Symptoms most frequently noted are apathy, dullness, drowsiness,[11] confusion or disorientation, and depression. Curiously enough, the more serious psychopathic phenomena are encountered in true Simmonds' disease.

It may be argued that these psychopathic phenomena are not traceable directly to diminished pitui-

TABLE 6. FREQUENCY OF LOSS OF LIBIDO AND POTENCY

Group (males)	Male cases in which specific mention was made
A (35 typical, verified cases)	19 (59%)
B (30 typical cases, not verified)	20 (72%)
C (40 suggestive cases)	21 (57%)
H (2 cases of anorexia nervosa)	0

[10] Nicolle (415), in attempting to differentiate Simmonds' disease and anorexia nervosa, stated that amenorrhea is usually a late event in Simmonds' disease, but according to the data compiled here this is not true.

[11] Pennetti (172) has noted somnolence in hypopituitarism and suggested a relation to hibernation in animals. May and Robert (340) believe that crises of somnolence point to disturbance of the nervous centers at the base of the brain.

tary function but are better interpreted as the natural consequences of weakness, cachexia, and profound metabolic disturbances. Weiner (206), stated that hypoglycemia and avitaminosis may be responsible for the mental symptoms. Nonetheless, that some of the patients with verified Simmonds' disease have been confined in institutions for the mentally abnormal is stressed here because of the difficulty noted in differentiating anorexia nervosa from true Simmonds' disease, a difficulty that is not diminished by encountering outspoken psychic disturbances in the verified cases. Nicolle (415), however, in 1939 attempted to differentiate the psychic manifestations of the two conditions by describing weakness, lethargy and somnolence as more characteristic of Simmonds' disease in contrast to the morbid energy and obstinacy exhibited by patients suffering from anorexia nervosa.

Anorexia. As is to be expected, the symptom anorexia, is far more striking in anorexia nervosa than in the verified cases of Simmonds' disease. It is mentioned more than twice as frequently in the former cases. However, loss of appetite does not exclude true Simmonds' disease.

The above items constitute the characteristics encountered in the anamnesis which we have considered of sufficiently outstanding interest to warrant inclusion in the published tables. The following items collated from careful reading of the case protocols are less crucial but are nonetheless interesting.

Possible inciting factors. In 13 of the 101 cases (13%) in which the diagnosis of Simmonds' disease was verified at autopsy, the onset of the disease seemed to follow or coincide with an infectious process not associated with pregnancy. No particular type of infection predominated, but a wide variety has been listed, including meningitis, 'pulmonary infections,' influenza, malaria and tularemia. In 17 (11%) of the 158 cases in *group B*, which were typical clinically but not verified, the disease began with an infection. In this group the occurrence of syphilis, osteomyelitis, rheumatic fever, catarrhal jaundice, diphtheria, dysentery and encephalitis was also mentioned. In the suggestive *group C*, 13 of the 180 cases (7% included an infection associated with onset of the disease. In only one of the cases of anorexia nervosa listed here did the onset coincide with an infection. Although infectious disease is not a frequent cause of pituitary cachexia, a serious infection immediately preceding the onset would lead to the assumption that true pituitary pathology exists.

Of much greater significance from the etiological standpoint is the part played by pregnancy. Pregnancy occurred just prior to the onset of the disease in 27 of the 67 verified female cases (42%). In over half of these (14 of 27 cases) abnormal hemorrhage at the time of delivery was specifically alluded to in the case report. In this connection it is pertinent to call attention to the observations of Sheehan (386, 4:6, 124) and Sheehan and Murdoch (287, 289, 290). From clinical and pathologic studies they concluded that the pituitary undergoes a rapid involution at the time of the puerperium. They assumed that a sudden reduction of blood flow to the gland takes place and that, if this is complicated by a circulatory collapse due to hemorrhage, the blood flow may be reduced almost to nothing. Thrombosis may thereby be precipitated in the sinuses of the gland with consequent infarction and necrosis. In 8 of the 27 cases (30%) sepsis occurred, with and without hemorrhage at delivery. However, Sheehan believed that the pituitary damage in such circumstances takes place before sepsis has had time to develop and is more likely due to hemorrhage and collapse.[12]

In 17 of the 128 females in *group B* (13%) pregnancy was considered the inciting factor. Twelve of these were associated with hemorrhage and in 4 sepsis was mentioned. The figures for *group C* were as follows: parturition as a possible cause of onset was

[12] Effkemann and Müller-Jäger (417) were able to follow up the cases of 84 women who had lost 800 to 1600 cc. of blood at parturition. Their cases were painstakingly tabulated with special emphasis on symptoms and were then separated into 3 groups according to the amount of blood lost. These statistics seemed to indicate that among the 20 patients who had lost between 1200 and 1600 cc. of blood, 60% showed diminished menstrual function and 50% remained sterile. However, 40% of the 20 patients became obese, whereas only 10% became thin. These observations are reminiscent of what happens in women following the menopause: most of them show a tendency to gain weight while the minority tends to shrivel. The causes of these phenomena are not known.

Although there is no experimental proof that the pituitary is indispensable to life (indeed, there is evidence to the contrary), under certain conditions acute pituitary inadequacy may be responsible for rapid collapse and death. Naturally, under such circumstances there is insufficient time for the development of Simmonds' disease. For example, Brown and Eder (418) reported the case of a 43-year-old primipara who had hypertension and albuminuria and was delivered by forceps after 16 hours of labor. The placenta was retained and expressed later. The patient suffered severe collapse with only moderate loss of blood. Despite stimulants and two blood transfusions the temperature rose to 104° F., the systolic blood pressure dropped from 184 to 60 and the patient died 4 days later. At autopsy the adrenals and ovaries were normal. The pituitary weighed 1 gm. and the anterior lobe stained poorly (necrobiosis) and contained areas of frank necrosis resembling infarction. Gotshalk and Tilden (419) reported a similar case.

Another example of acute infarction of the pituitary followed by death within 24 hours was reported by Kotte and Vonderahe (420) under the title, "The Houssay phenomenon in man." Their patient had had diabetes mellitus for 5 years and in the 2 months prior to death signs of tuberculosis had developed. He was brought into the hospital in a semi-stuporous state with a temperature of 102.8° F. Four+ glycosuria had been noted the day before, but 24 hours later no sugar was found in the urine; the blood sugar was 31 mg.% and later below 20 mg.%, also in the spinal fluid. Autopsy disclosed an infarction involving almost the entire anterior lobe of the pituitary.

noted in 40 of the 131 female cases (31%). Hemorrhage was reported in 23 of these 40 cases (58%) and sepsis in 6 (15%). In none of the 20 cases of anorexia nervosa assembled for comparison was any mention made of parturition as an inciting factor; in fact, the majority of the patients were young unmarried females.

One may conclude, therefore, that when either parturition or a severe acute infection is followed by progressive loss of weight with asthenia, amenorrhea and a low basal metabolic rate, true pituitary damage exists.[13] Admittedly, in a large number of these cases no such clue to onset can be elicited and the origin of the disease remains a mystery. However, there are likewise no adequate explanations for the origin of many other endocrinopathies, such as the onset of acute diabetes mellitus in childhood without apparent inciting cause. A familial incidence was noted only in the case of Zondek (25, 157).

TABLE 7. DURATION

Group	Cases in which data were given	No. of cases, of duration				Length of Time		
		1 yr. or less	2–5 yr.	6–10 yr.	Over 10 yr.	Max. yr.	Min. mo.	Av. yr.
A (101 typical, verified cases)	90 (89%)	20	28	19	23	44	5	7.9
B (158 typical cases, unverified)	128 (81%)	48	60	17	9	30	2	3.1
C (180 suggestive cases)	141 (78%)	44	54	23	20	40	2 days	5.2
H (20 cases of anorexia nervosa)	20 (100%)	6	12	2	0	8	5	2.78

In the cases reported by Cyran (395), Rouvillois, Reverchon et al. (309, 310), and Reinhardt (398), the onset of the disease apparently followed a head injury. Also Homer Rush (295), in a personal communication, described a typical case in which the onset followed fracture of the skull. One of our patients whose case is reported for the first time in this paper (*case 4* in Case Summaries) developed a suggestive clinical picture following a head injury which caused an internal carotid aneurism. Tying off the carotid on the affected side resulted in some amelioration of symptoms.

Duration. Table 7 has been compiled in order to determine how long definite symptoms had been present before the patient consulted the author of the report. In gathering these statistics, the various items were recorded separately for each sex, but as there were no noteworthy differences in duration in males and females, these more detailed figures were omitted.

The following points seem to deserve comment. In *groups* A, B, and C the symptoms may exist for a long time, the maximum being 44, 30 and 40 years respectively. Accordingly, even though the condition ends fatally, it may run a long course. In the verified group the duration of symptoms prior to consulting the author averaged 7.9 years, while in the unverified group the average was 3.1 years. In this connection it should be noted that 46 per cent of the cases in which autopsies were performed were reported prior to 1930 while less than 16 per cent of the cases without records of autopsies appeared before that time. This finding may imply that a more widespread acquaintance with the disease has resulted in its earlier recognition. The course may be swift or may extend over many years. Apparently the duration of the disease depends upon the type of underlying lesion, as for instance a malignant tumor, and perhaps especially upon the degree of secondary adrenal incapacity.

TABLE 8. PREGNANCY BEFORE ONSET OF THE DISEASE

Group (Females)	Cases with previous pregnancies	Number of previous pregnancies		
		1	2–5	Over 5
			no. of cases	
A (65 typical, verified cases)	30 (46%)	3	15	12
B (128 typical cases, unverified)	18 (14%)	4	11	3
C (131 suggestive cases)	42 (32%)	10	23	9
H (18 cases of anorexia nervosa)	1 (6%)	0	1	0

Pregnancy before and after onset of disease. (*Table 8*). Of the 65 females in *group A*, 30 (46%) had one or more pregnancies prior to the onset of the disease. Indeed, 12 of these 30 were pregnant over 5 times and occasional reports of 9 and 11 pregnancies were found. As might be expected, pregnancy rarely occurs after the onset of the disease. In the typical verified cases of *group A*, pregnancy occurred in only one instance after onset (164, *case 1;* 165, *case 2*; 166). However, Sheehan (386, 416, 124) and Sheehan and Murdoch (289, 290) have recorded several cases in which the clinical picture was relatively mild and a subsequent pregnancy with its concomitant anterior pituitary hyperplasia had a decidedly favorable effect (autotherapy) (287, *case 5;* 289, *cases 1, 2, 4, 7, 8;* 290, *cases 2, 4;* 386, *case 12*).

Cold intolerance. Forty-one of the 101 patients in *group A* (41%) complained of intolerance to cold weather. Fifty-two of the 158 patients in *group B*

[13] Nicolle (415) contended that the onset of Simmonds' disease is abrupt in contrast to the gradual appearance of the symptomatology an anorexia nervosa. This may be true when Simmonds' disease develops rather promptly after a severe infection or consequent to hemorrhage at parturition, but the distinction does not hold, for example, when the pathological cause is a pituitary tumor.

(33%) and 27 per cent of the patients in *group C* made the same complaint. However, in only 3 of the 20 cases of anorexia nervosa was this symptom recorded.

This symptom could be interpreted, in association with the profoundly low basal metabolic rate, as a secondary hypothyroid phenomenon, but it should also be recalled that adrenalectomized animals and patients with Addison's disease are extremely sensitive to low temperatures. The secondary deficiency of adrenal cortical function which undoubtedly occurs in Simmonds' disease should be considered as a possible factor. Patients with anorexia nervosa supposedly do not have thyroid or adrenal deficiency, yet they occasionally suffer from cold intolerance, though less frequently than the patients in the other groups. Upon further statistical analysis it was found that patients with cold-intolerance did not disclose on the average lower basal metabolic rates, blood pressures, hemoglobin levels or red blood cell counts than the average figures for the entire groups.

Associated diseases and miscellaneous symptoms. Table 9 presents in considerable detail a number of diseases that have been reported in association with Simmonds' disease. These may or may not have had any relation to the onset or course of Simmonds' disease, but because of their frequent occurrence they are recorded here. In addition, a number of miscellaneous symptoms are recorded which did not appear sufficiently important to be included in the extensive tables of case reports.

TABLE 9. ASSOCIATED DISEASES AND MISCELLANEOUS SYMPTOMS

Disease or Symptom	*Group A* (101 typical verified cases)			*Group B* (158 typical cases, not verified)			*Group C* (180 suggestive cases)			*Group H* (20 cases of anorexia nervosa)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tuberculosis (active or quiescent)	7(20%)	11(17%)	18(18%)	2(7%)	3(2%)	5(3%)	2(5%)	4(3%)	6(3%)	0	0	0
Syphilis (clinical, serological or in history)	5(14%)	8(12%)	14(14%)	0	5(4%)	5(3%)	3(7%)	6(5%)	9(5%)	0	0	0
Diabetes Mellitus	0	1(2%)	1(1%)	0	0	0	0	1(1%)	1(1%)	0	0	0
Diabetes Insipidus	8(23%)	7(11%)	15(15%)	6(20%)	9(7%)	15(10%)	11(28%)	6(5%)	17(9%)	0	1(6%)	1(5%)
Oliguria	2(6%)	4(6%)	6(6%)	1(3%)	6(5%)	7(4%)	1(2%)	8(6%)	9(5%)	0	0	0
Edema, including	6(17%)	12(18%)	18(18%)	2(7%)	14(10%)	16(10%)	3(7%)	11(8%)	14(8%)	0	4(22%)	4(20%)
Ascites and	2	1	3	0	1	1	0	2	2	0	1	1
Pleural Fluid	2	1	3	0	0	0	0	0	0	0	0	0
Gastrointestinal Symptoms excluding anorexia, including	20(57%)	35(54%)	55(54%)	16(53%)	82(64%)	98(62%)	12(30%)	70(53%)	83(46%)	1(50%)	12(67%)	13(65%)
indigestion	1	1	2	1	15	16	0	0	0	1	4	5
pain	5	9	14	1	13	14	3	23	26	0	1	1
cramps	0	1	1	0	3	3	0	4	4	0	0	0
nausea	4	3	7	4	5	9	3	6	9	1	0	1
vomiting	13	20	33	8	22	30	8	24	32	0	4	4
diarrhea	3	5	8	1	4	5	3	6	9	0	0	0
constipation	6	19	25	7	49	56	1	32	34	0	6	6
Voracious Appetite	0	1(2%)	1(1%)	0	2(2%)	2(1%)	0	1(1%)	1(1%)	0	0	0
Headache	15(43%)	16(25%)	31(31%)	10(33%)	26(20%)	36(23%)	11(28%)	33(25%)	44(24%)	0	1(6%)	1(5%)
Vertigo and / or Fainting	6(17%)	11(17%)	17(17%)	4(13%)	16(12%)	20(13%)	7(17%)	30(23%)	37(21%)	0	1(6%)	1(5%)
Epilepsy or Convulsions	2(6%)	6(9%)	8(8%)	1(3%)	2(2%)	3(2%)	0	1(1%)	1(1%)	0	0	0
Youthful Appearance	2(6%)	0	2(2%)	0	3(2%)	3(2%)	2(5%)	5(4%)	7(4%)	0	0	0

Tuberculosis is of such common occurrence that one would expect to encounter it now and again even in as rare a malady as Simmonds' disease. However, that it should have been noted as either quiescent or active in 18 per cent of the verified cases is somewhat surprising. In a few of these it occurred in the pituitary body itself. The discrepancy between this incidence of 18 per cent and the minimal occurrence of tuberculosis in *groups B* and *C* as well as its complete absence in the 19 cases of anorexia nervosa is noteworthy. One might deduce from these findings that malnutrition alone does not render a patient more vulnerable to tuberculosis. This conclusion is borne out

by the extreme rarity of tuberculosis as a complication of hyperthyroidism, a disease in which weight loss is conspicuous.

The incidence of syphilis does not vary markedly in *groups A, B* and *C*. Here again actual gumma of the hypophysis has been reported in a few cases as the outstanding pathological finding. The blood serum in 46 cases in *group A*, 42 cases in *group B* and 41 cases in *group C*, was tested for syphilis by the Wassermann, Kahn or Hinton reaction. The positive tests in these instances were: 15 per cent in *group A*, 14 per cent in *group B* and 12 per cent in *group C*. The spinal fluid Wassermann was positive in 2 of 18 cases in *group A*, in 1 of 10 cases in *group B* and in 1 of 14 cases in *group C*. Therefore, syphilis of the central nervous system, as evidenced by positive spinal-fluid tests, may be considered a negligible factor in all three groups. The role of syphilis as a causative factor in Simmonds' disease is not impressive.[14]

The incidence of diabetes insipidus in *groups A, B* and *C*, namely 15, 10 and 9 per cent respectively, cannot be ignored since this disease itself is rare. The important investigations of Ranson and co-workers suggest that a lesion in the neural pathway from the supraopticus nucleus to the posterior pituitary, or a deficient production of the pars intermedia-posterior lobe antidiuretic hormone must be held responsible. Probably this complication would occur even more frequently if the pathologic alterations causing Simmonds' disease did not involve principally the anterior pituitary.

Apparently the water balance in Simmonds' disease can be upset in either direction, for oliguria has been noted occasionally.

The occurrence of edema in *group A* is noteworthy, though it was reported less frequently in *groups B* and *C*. A study of the correlated findings seems to exclude its cardiac or renal origin in most of the cases. Perhaps the explanation is similar to that for hunger edema with lowered blood proteins which was suggested by Brugsch in discussing the paper of Zondek (156). Accumulation of fluid in the body cavities (ascites and pericardial or pleural effusion) may be merely an internal manifestation of this same condition. Incidentally, these complications have been discovered occasionally in myxedema as reported by Mussio-Fournier (421), Hertzler (422), Evans (423), ourselves (424), and Hanssen (425).

Even when anorexia is excluded, the various gastrointestinal symptoms occur with about equal frequency in all four groups, namely 54, 62, 46 and 65 per cent respectively. Further details are shown in table 9. There is nothing characteristic about these symptoms, however, that would help in differential diagnosis. Evidently they are associated with malnutrition and asthenia of psychic, pituitary or adrenal origin. On the whole, they are by no means as conspicuous as in Addison's disease.

[14] A case somewhat suggestive of Simmonds' disease, but in which a normal BMR was found was reported by Falta in 1925 (76).

PHYSICAL FINDINGS

Cachexia or emaciation. The outstanding symptom, emaciation, inspired the descriptive designation, 'hypophyseal cachexia.' Analysis of the reports shows that it was a striking characteristic in 65 per cent of the cases in the verified group, in 58 per cent of the cases typical clinically, and in 75 per cent of the cases recognized as anorexia nervosa, In *group C*, in which the diagnosis of Simmonds' disease was suggestive but some of the cardinal characteristics were absent, cachexia occurred in only 25 per cent of the cases. This observation increases the doubt as to the correctness of the diagnosis of Simmonds' disease in many of the cases in *group C* although the postmortem findings in several of them were quite characteristic. It is reasonable to assume that this disease, like most others, may occur in varying degrees of severity and may at times display only a partial clinical picture. The incidence of cachexia was statistically analyzed according to sex and no noteworthy difference was found in any of the groups. A striking atrophy of the tissue of the buttocks was noted in several of the cases in our series in which the emaciation was advanced.

A careful study of 40 undernourished persons was published by Kerppola in 1939 (361). He found that one-half of his group showed an increased glucose tolerance, relative lymphocytosis and low gastric acidity; one-third showed a slightly small sella turcica, slight anemia and granulocytopenia; one-fourth of 35 females had menstrual disturbances; one-eighth of the group had basal metabolic rates of -20% or under (we have included these 5 cases in *group C*). Kerppola concluded that only 5 of these 40 thin persons showed evidence of 'pituitary weakness.' As remarked before, this study raises the question as to whether there may not be a mild form of Simmonds' disease.

Amount underweight. (*Table 10*). The amount under ideal weight could be calculated only when the patient's age, sex, height, and weight were given in the case report. The resulting calculations give a fairly accurate demonstration of the degree of undernutrition. The most extreme instance was reported by Mertz (178, *case 1*), a verified case of Simmonds' disease in a male who was 47.5 kg. (104 lb.) underweight.

Premature senility. (See table 11 for classification of

TABLE 10. AMOUNT UNDERWEIGHT FROM NORMAL STANDARDS

Group	Cases in which calculation was possible	Amount Underweight		
		Maximum	Minimum	Average
A (101 typical, verified cases)	32 (32%)	47.5 kg. (104 lb.)	6.1 kg. (13 lb.)	21.2 kg. (47 lb.)
B (158 typical cases, not verified)	97 (61%)	36.5 kg. (80 lb.)	0	20.7 kg. (46 lb.)
C (180 suggestive cases)	73 (41%)	37.6 kg. (83 lb.)	1 kg. (2 lb.)	17.2 kg. (38 lb.)
H (20 cases of anorexia nervosa)	19 (95%)	26.8 kg. (59 lb.)	10 kg. (22 lb.)	20.7 kg. (46 lb.)

cases in which definite mention of this symptom was made). Evidently premature ageing is more characteristic of organic disturbance, for it occurs in true Simmonds' disease with far greater frequency, especially in the male, than it does in the functional psychosis of anorexia nervosa. Thomson (355) has included striking photographs of premature senility in a recent case report.

Loss or absence of axillary and/or pubic hair. (See table 12 for classification of cases in which definite mention of these symptoms was made.) Again, this striking phenomenon is far more likely to occur in true Simmonds' disease than in anorexia nervosa. It is probably due to the deficient secretion of the anterior pituitary gonadotropic hormone which results in secondary gonadal insufficiency. No doubt 'exceptions prove the rule'; but it must be noted that such loss of sexual hair has been reported in anorexia nervosa, and contrariwise, overabundant body hair has been reported in cases of verified Simmonds' disease, as in a case personally observed by the authors (125, *case 2;* 126, *case 1*). Herrick (22) and Nicolle (415) insisted that loss of body hair is an important diagnostic sign.

Naturally, uncomplicated cases of alopecia totalis cause no confusion in differential diagnosis. However, axillary and pubic hair may be lost in cases of hemosiderosis with cirrhosis of the liver and spleen and in cases of secondary atrophy of the thyroid, adrenals

TABLE 11. FREQUENCY OF PREMATURE SENILITY

Group	Male	Female	Total
A (101 typical, verified cases)	46%	45%	45%
B (158 typical cases, not verified)	47%	26%	30%
C (180 suggestive cases)	12%	10%	10%
H (20 cases of anorexia nervosa)	0	6%	5%

TABLE 12. LOSS OR ABSENCE OF AXILLARY AND / OR PUBIC HAIR

Group	Males	Females	Total
A (101 typical, verified cases)	80%	82%	80%
B (158 typical cases, not verified)	77%	53%	58%
C (180 suggestive cases)	43%	60%	53%
H (20 cases of anorexia nervosa)	0	17%	15%

and gonads (426). Althausen and Kerr (427, 428) have called attention to the secondary sexual hypoplasia in cases of hemochromatosis. Their patients (all males) showed thinning of the beard so that shaving was required less frequently, together with loss of hair from the axillae and chest and thinning of the pubic escutcheon so that it resembled the female type.

Sheldon (131), like many others, agreed that anorexia nervosa and the physical changes caused by famine may simulate the 'clinical tableau' of Simmonds' disease. In attempting to differentiate between the functional and organic diseases, he stated that "an increased growth of hair has never been described in any of the case reports of Simmonds' disease, whereas it is frequent in anorexia nervosa" and has been reported as a result of widespread famine. Furthermore, he stated that hypertrichosis has a "teleological significance—to assist in preserving the body heat." Though this hypothesis is most intriguing, we must again point out that one of our own patients in whom the diagnosis was verified by autopsy (125, *case 2;* 126, *case 1*) displayed an overabundance of downy body hair.

Genital atrophy or infantilism. (See table 13 for classification of cases in which definite mention of these symptoms was made.) This truly objective finding occurs with about equal frequency in all groups. It is no doubt associated, as part of the same process consequent to gonadal deficiency, with amenorrhea, loss of libido and potency, loss of sexual hair, and premature senility. Its apparently greater frequency in males is probably explained by external obviousness. However, absence of atrophy does not necessarily

TABLE 13. GENITAL ATROPHY OR INFANTILISM

Group	Male	Female	Total
A (101 typical, verified cases)	60%	42%	49%
B (158 typical cases, not verified)	60%	23%	34%
C (180 suggestive cases)	38%	39%	37%
H (20 cases of anorexia nervosa)	0	44%	40%

preclude deficient function. Furthermore, even a severe degree of genital atrophy (and more or less loss of sexual hair and premature senility) may occur as a result of almost any wasting disease. For example, Bauer (429) reported these findings in a case of chronic sprue, but he ascribed them to a secondary pituitary deficiency and commented on the resemblance of the clinical picture in his case to Simmonds' disease. A striking discrepancy was, however, an elevated basal metabolic rate.

Blood pressure. Study of table 14 reveals that some of the patients in *groups A, B* and *C* had mild hypertension. On the other hand, some patients in all three groups had severe hypotension, almost as low as in grave cases of Addison's disease. However, the average systolic blood pressure in these groups was not conspicuously different from that occasionally found in normal or slightly asthenic individuals.[15]

A detailed statistical analysis reveals that a systolic pressure under 90 mm. Hg was found in 38 per cent of the cases in *group A*, in 44 per cent of the cases in *group B*, in 27 per cent of the cases in *group C* and in 50 per cent of the cases in *group H*. In summary one is forced to conclude that the hypotension in these cases is concomitant merely with the malnutrition, and is not nearly as marked as in Addison's disease.

TABLE 14. BLOOD PRESSURE

Group		Cases in which data were given	Max.	Min.	Av.
			Values in mm. Hg		
A (101 typical, verified cases)	Systolic	68 (67%)	160	50	96
	Diastolic	47 (47%)	100	40	62
B (158 typical cases, not verified	Systolic	122 (77%)	142	60	91
	Diastolic	98 (62%)	100	0	61
C (180 suggestive cases)	Systolic	131 (73%)	160	55	98
	Diastolic	100 (56%)	110	0	65
H (20 cases of anorexia nervosa)	Systolic	20 (100%)	108	72	89
	Diastolic	20 (100%)	82	40	59

Additional interesting physical findings not considered of sufficient importance to be included in the tables are given below.

Interference with growth (height). The height of 42 adults in *group A* was recorded. Only one of these was under 4 feet, 10 inches. In *group B*, 8 out of 99 adults, and in *group C* 9 of 88 adults were below this height. It seems reasonable to assume that in these patients the anterior pituitary deficiency began in childhood and therefore a degree of dwarfism resulted. But, as mentioned in the discussion of age, true Simmonds' disease is a disease of adult life and only occasionally arises before puberty. Therefore dwarfism is a rare phenomenon. The anterior pituitary deficiency of childhood, 'hypophyseal infantilism,' which is characterized by retardation of growth and sexual infantilism without adiposity, is by no means uncommon and never proceeds to a fatal termination unless caused by a tumor. Oddly enough, 2 girls aged 15 and 16 years respectively, who were considered as having anorexia nervosa, were less than 4 feet, 8 inches in height.

[15] Schellong (324, 323, 406) has emphasized that the drop in blood pressure with change of posture and also following exercise is marked in Simmonds' disease. However, since this tendency to postural hypotension may occur in other states, including malnutrition, it is hardly specific for Simmonds' disease.

TABLE 15. FREQUENCY OF OCCURRENCE OF DRY SKIN, LOSS OF NONSEXUAL HAIR, DECAY OR LOSS OF TEETH

Group	Dry Skin	Loss of Hair of Eyebrows, Scalp, Beard	Decay or Loss of Teeth
A (101 typical, verified cases)	55 (54%)	51 (50%)	42 (42%)
B (158 typical cases, not verified)	81 (51%)	56 (35%)	33 (21%)
C (180 suggestive cases) cases)	67 (37%)	70 (39%)	34 (19%)
H (20 cases of anorexia nervosa)	5 (25%)	1 (5%)	2 (10%)

Dry skin. Loss of non-sexual hair. Decay or loss of teeth. (See table 15 for classification of cases in which specific mention of these symptoms was made.) Dryness of the skin is attributable either to secondary hypothyroidism or to inanition. Loss of nonsexual hair, dental caries and occasional loss of teeth are probably of trophic origin; yet it is a curious circumstance that these changes have rarely been reported in anorexia nervosa in which malnutrition is equally pronounced.[16]

Pulse. In 9 of the 42 cases (21%) of *group A* in which the pulse rate was mentioned, a definite bradycardia of 60 beats per minute or less was noted. The same was observed in 25 of 60 cases in *group B* (42%), and in 5 of 16 cases (31%) in *group H*. For some reason bradycardia of this degree was exceptional in *group C* (8% of 47 cases). The slow pulse rate may be related to the lowered basal metabolic rate, but since the latter is so consistently low, it is surprising that bradycardia does not occur more frequently. May, in discussing a paper on 'anorexie mentale' by Mollaret and Peron (430), stated that bradycardia did not occur in this condition and that its presence favored a diagnosis of Simmonds' disease. Our statistics do not bear out this observation (see section on differential diagnosis).

Temperature. A markedly subnormal temperature (35.5°C. or 96°F. or under) was noted in 13 of 37 cases (35%) of *group A*, in 8 of 57 cases (14%) of *group B*, in 4 of 29 cases (14%) of *group C*, and in 2 of 15 cases (13%) of *group H*. This obvious discrepancy forces one to assume that marked hypothermia in a patient who has cachexia, asthenia, loss of sexual function and a lowered basal metabolism, suggests the diagnosis of Simmonds' dis-

[16] Nicolle (415) stated that loss of body hair and loss of teeth have never been seen in aorexia nervosa. Use of the word 'never' seems an exaggeration.

ease rather than that of anorexia nervosa. Here also, it is somewhat surprising that a low temperature is not encountered more frequently, especially in *groups* A and B in which the basal metabolic rates are consistently low.

Pigmentation. In less than one-third of the verified cases (24%) some degree of pigmentation, varying in intensity from yellow to brown, was mentioned. It was less frequent in the other groups. This pigmentation may be

TABLE 16. BASAL METABOLIC RATE

Group	Cases in which data were given	Max.	Min.	Av.
A (101 typical, verified cases)	41 (41%)	−17%	−51%	−33%
B (156 typical cases, not verified	121 (72%)	−20%	−67%	−35%
C (180 suggestive cases)	110 (61%)	+40%	−52%	−18%
H (20 cases of anorexia nervosa)	20 (100%)	−14%	−51%	−29%

ascribed to adrenal involvement (in view of the pronounced pigmentation seen in Addison's disease) and perhaps the same explanation may be given for its occurrence in many cases of outright myxedema. However, that the characteristic pigmentation of Addison's disease is due directly to suprarenal deficiency has never been proved. On the contrary, it does not vanish, as a rule, upon administration of either the cortical or medullary adrenal hormone. Zondek's finding of a pigmentary factor in the pars intermedia which acts on the melanophores of the skin is intriguing in this connection, but it seems premature to ascribe the pigmentation occasionally seen in Simmonds' disease directly to the hypophysis. Berkman (431), in describing the clinical findings in 117 cases of anorexia nervosa, mentioned that brownish discoloration of the skin was noted in 12 cases.

Pallor was mentioned in 48 per cent of the cases in *group A*, in 23 per cent of the cases in *group B*, and in 23 per cent of the cases in *group C*. In the cases of anorexia nervosa no pallor was noted.

Goiter was exceedingly rare in all groups. This is not surprising inasmuch as secondary atrophy rather than overgrowth of the thyroid would be expected.

Atrophy of the breasts. Probably the general body emaciation so overshadowed the condition of the mammary glands that their atrophy was accepted as part of the tissue-wasting process. Yet mammary atrophy, as distinguished from mere loss of fat in the breast, would be expected as part of the loss of sexual function. It was mentioned specifically in only 23 per cent of the 65 females in *group A*, in 8 per cent of the 128 females in *group B*, in 11 per cent of the 131 females in *group C*, and in only one instance in the 18 cases of thin women diagnosed as anorexia nervosa.

Laboratory Findings

Basal metabolic rate. From the perusal of table 16 it is obvious that a markedly low basal metabolic rate characterizes both the verified and the unverified cases of Simmonds' disease as well as those frankly recognized as anorexia nervosa. The lowest levels reached in *groups* A, B and H (−51%, −67%, and −51%) are quite as low as those encountered in severe myxedema. One is tempted to postulate that a deficiency of the thyrotropic fraction from the anterior pituitary is responsible for the low rate, but against such an assumption is the failure to affect clinical improvement in the majority of these patients by the administration of thyroid substance in either true Simmonds' disease or anorexia nervosa. More likely, then, is the conception that the lowered metabolism is a result of malnutrition.

Fasting blood sugar. (*Table 17*). In addition to the foregoing data, further analysis discloses that in 43 per cent of the 42 cases in *group A* a fasting blood sugar of 60 mg.% or under was reported whereas only 14 per cent of the 96 cases in *group B*, 7 per cent of the 83 cases in *group C*, and 21 per cent of the 14 cases in *group H* showed comparably low values. The presence of fasting hypoglycemia, together with the four cardinal characteristics (emaciation, asthenia, low basal metabolic rate and loss of sexual function), is therefore suggestive of true Simmonds' disease.

TABLE 17. FASTING BLOOD SUGAR

Group	Cases in which data were given	Max.	Min.	Av.
		Values in mg. %		
A (101 typical, verified cases)	42 (42%)	114	24	66
B (158 typical cases, unverified)	96 (61%)	138	36	79
C (180 suggestive cases)	83 (46%)	153	35	82
H (20 cases of anorexia nervosa)	14 (70%)	134	26	73

Glucose tolerance tests. Glucose tolerance tests were reported in 21 of the 101 verified cases (21%). Of these 8 were interpreted as normal, 2 as diabetic in type and 11, or 65 per cent, as 'flat' (showing increased tolerance).

In *group B*, glucose tolerance tests were reported in 59 of 158 cases (37%). Of these 17 were interpreted as normal, 11 were considered to show mild or frank diabetic tendencies and 21 showed the opposite state of increased tolerance as exemplified by a flat curve.

Ten others at some point during the test reached a definitely hypoglycemic level. In other words, normality, diabetic tendency, increased tolerance, and an occasional hypoglycemic level were fairly evenly distributed.

Glucose tolerance tests were reported in 47 of the 180 suggestive cases (26%). A study of these tests showed a spread similar to that found in the previous group.

In 12 of the 20 cases of anorexia nervosa (60%) glucose tolerance tests were recorded. In 6 cases of the 12 (50%) the tolerance for glucose was increased. However, this number may be too small to have any significance.

Sensitivity to insulin was rarely mentioned (*group A*, 7%; *group B*, 8%; *group C*, 4%; and *group H*, 0%). Hypoglycemic coma occurred in 5 per cent of the verified cases and only once in *group C*; it was not mentioned in *groups B* and *H*. In view of the Houssay and Biasotti experiments on dogs (432) and the likelihood that a contrainsular or diabetogenic hormone is elaborated in the anterior pituitary, it is interesting to note that frank diabetes mellitus has been reported in but one case of verified Simmonds' disease. Theoretically this observation would harmonize with the concept that deficient anterior pituitary function leads to hypoglycemia rather than hyperglycemia and it is borne out further by the fact that definite hypoglycemic coma was reported in 4 cases.[17]

TABLE 18. HEMOGLOBIN. RED BLOOD CELL COUNTS. EOSINOPHILES

	Group A (101 typical, verified cases)	*Group B* (158 typical cases, unverified) unverified	*Group C* (180 suggestive cases) cases)	*Group H* (20 cases (20 cases nervosa) nervosa)
Hemoglobin				
Cases in which data were given	57 (56%)	68 (43%)	71 (39%)	10 (50%)
Values				
Maximum	102%	103%	110%	105%
Minimum	40%	35%	21%	52%
Average	65%	76%	74%	82%
Red Blood Cells				
Cases in which data were given	59 (58%)	73 (46%)	74 (41%)	9 (45%)
Values/cu. mm.				
Maximum	5,600,000	5,800,000	5,600,000	5,190,000
Minimum	2,000,000	1,500,000	730,000	3,000,000
Average	3,710,000	3,980,000	3,800,000	4,150,000
Eosinophiles				
Cases in which data were given	41 (41%)	46 (29%)	59 (33%)	9 (45%)
Values				
Maximum	40%	12%	30%	2%
Minimum	0	0	0	0
Average	6.3%	2.6%	4.3%	0.6%

In addition to these data, which constitute the laboratory investigations listed in the tables, other interesting information collected from the 615 case protocols is appended hereto.

TABLE 19. GASTRIC ACIDITY

Group	Cases in which data are given	Achylia	Achlorhydria	Low free acid	Normal Normal	Hyperacidity
A (101 typical, verified cases)	20 (20%)	3	7	7	2	1
B (158 typical cases, unverified)	38 (24%)	5	11	5	14	3
C (180 suggestive cases)	33 (18%)	6	6	7	12	2
H (20 cases of anorexia nervosa)	2 (10%)	0	1	0	1	0

Hemoglobin, red blood cells and eosinophiles. (*Table 18*). Even though severe anemia is not characteristic of verified Simmonds' disease, the degree of anemia in *group A* was greater than that in *groups B, C* and especially *H*.[18]

It is interesting to note that the average percentage of eosinophiles is definitely above the normal level in *group*

[17] In this connection we call attention to the case reported by Anna Pettersson (77) under the designation "Hypoglycemia." The patient was a woman aged 33, 26 lb. underweight, with a systolic blood pressure of 90 mm. Hg. She had been amenorrheic for 6 years following her last pregnancy which had been complicated by hemorrhage. [Sheehan (386, 416, 124) and Sheehan and Murdoch (287, 289, 290) have noted pituitary damage in several instances in which death followed hemorrhage at parturition.] Pettersson's patient was first seen in hypoglycemic shock with a blood sugar of 25 mg.%. It was noted that she had lost considerable body hair as well as several teeth and that her nails were brittle and her skin was dry. At autopsy the pituitary was described as 'small' (no microscopic report was given); the ovaries were sclerotic, the thyroid was small and the islets of Langerhans showed mild hyperplasia. In our opinion this was probably a case of Simmonds' disease.

Rolleston (433) refers to Wilder (434) as having observed attacks of spontaneous hypoglycemia in Simmonds' disease, but a perusal of Wilder's paper reveals that his two patients were obese rather than cachectic and had menstruated normally. Certainly, they were not cases of Simmonds' disease. Wilder reported them as examples of a new syndrome, 'hypophyseal spontaneous hypoglycemia.'

In this connection certain experimental work is pertinent. Corkill, Marks and White (435) reported insulin sensitivity following hypophysectomy in rabbits, and Mahoney (436) reported hypoglycemia following removal of the pituitary in dogs.

[18] Snapper, et al. (352) reported several patients who showed some of the characteristics of Simmonds' disease such as loss of weight and sexual hair, in whom achlorhydria and pronounced anemia and even combined system disease developed subsequently. They believed the pituitary was initially responsible for the subsequent course. Van Bogaert (285) presented 2 patients with similar neurological lesions but without hyperchromic anemia. The gastric acidity in one of these patients was normal. He called the condition 'pituitary pseudo-tabes.'

A, whereas this is not the case in *groups B* and *C*, and emphatically not in *group H*. In 21 of the 41 cases (51%) in *group A*, eosinophilia of 5 per cent or over was noted, and in 9 of these the percentage was 10 to 40. It is difficult to appraise the significance of such an eosinophilia, especially since the same abnormality has been noted in the opposite pituitary state, acromegaly.

Gastric acidity. (*Table 19*). In about one-fifth of the verified cases gastric acidity was determined, and in 85 per cent of these either achylia, achlorhydria or low free acid was found. The same phenomenon was noted in *groups B* and *C*, but in only 55 and 58 per cent respectively. Comment is withheld regarding *group H* since gastric acidity was determined in only 2 of the 20 cases. However, Berkman (431) in reporting the clinical findings in 117 case of anorexia nervosa mentioned achlorhydria in 11 cases and a tendency to hypoacidity in the group as a whole. As has been stated, Snapper et al. (352) have advanced the interesting idea that achylia may result from hypofunction of the anterior pituitary and that it may later lead to pernicious anemia or even to combined system disease.

Plasma cholesterol. Although no sweeping conclusions can be drawn from the small number of cases in which the plasma cholesterol was determined, it is nonetheless interesting that the average level was slightly above normal in *groups A* and *C*, namely 234 mg.% and 238 mg.% respectively. The highest level attained was in a verified female case, namely 560 mg.%. No comparison can be made with anorexia nervosa as the plasma cholesterol was determined in only one case. A high blood cholesterol may be attributed to secondary hypothyroidism.

Other laboratory findings. The rather scanty data on nitrogen partition (non-protein nitrogen, blood urea nitrogen, uric acid, urea, creatinine, and blood proteins) disclosed no noteworthy abnormalities. A similar statement can be made concerning the fragmentary reports of blood sodium chloride,[19] chlorides, sodium, potassium, calcium, phosphorus and carbon dioxide combining power, as well as electrocardiograms.[20]

Sella turcica. Roentgenograms of the sella turcica were obtained in 42 per cent of the cases in *group A*, 61 per cent of those in *group B*, 42 per cent of those in *group C* and 55 per cent of those in *group H*. All roentgenograms in *group H* were considered normal. However, in 18 of the 42 cases in *group A* (43%), in 21 of the 96 cases in *group B* (22%) and in 18 of the 75 cases in *group C* (24%) enlargement, destruction, or calcification of the sella was evident. This finding would lead to the suspicion that a tumor,[21] a cyst or a chronic infectious process is the underlying pathologic lesion in these cases. Such a condition, therefore, in an emaciated asthenic patient who has lost sexual function and has a low metabolic rate would be strong evidence in favor of true Simmonds' disease.

TABLE 20. COURSE OF DISEASE AND RESPONSE TO TREATMENT

Group	Number of patients						
	Dead	Unimproved	Slightly improved	Temporarily rarily improved	Improved	Much improved	Spontaneously improved
A (101 typical, verified cases)	98 (97%)	28 (28%)	4 (4%)	20 (20%)	5 (5%)	1 (1%)	0
B (158 typical cases, unverified)	8 (5%)	16 (10%)	19 (12%)	9 (6%)	75 (47%)	21 (13%)	3 (2%)
C (180 suggestive cases)	36 (20%)	15 (8%)	23 (13%)	8 (4%)	59 (33%)	18 (10%)	2 (1%)
H (20 cases of anorexia nervosa)	1 (5%)	3 (15%)	0	0	9 (45%)	8 (40%)	0

COURSE

Reaction to treatment. (*Table 20*). Naturally, the outlook for the effectiveness of any therapeutic endeavors would be most unfavorable if the verdict depended on the results of treatment in the 101 patients of *group A*, since nearly all of them died.[22] The duration of life may have been prolonged somewhat in a few of these patients by glandular therapy, but in many of them it was of no help whatever. Many varieties of pituitary preparations of the whole gland or of the anterior lobe only were tried, both orally and hypodermically. Thyroid substance, thyroxin, adrenal, ovarian and testicular extracts, gonadotropins and insulin were used. Whereas these hormones almost never prevented a fatal outcome in the group of 101 verified cases, they produced astounding improvement in 60% of comparable cases in *group B*.

The argument may be advanced that Simmonds' disease may vary in severity, that possibly a fortunately potent batch of gland extract may have been available or that the dosage may have been large and the treatment more persistent in some of the cases in which favorable responses were noted. However,

[19] Meyer (95) reported a lowered sodium chloride in 5 out of 8 cases.

[20] Sheehan (124) stated that low voltage in the electrocardiogram is a frequent finding in Simmonds' disease.

[21] Horrax (22) stated that symptoms of Simmonds' disease are frequently noted in neurosurgical clinics and interpreted as due to the pressure of pituitary adenomata; following removal of the adenomata marked improvement may occur. A patient of De Martel and Guillaume (206) showed marked improvement after surgical drainage of a 'cholesteatomatous pseudo-cyst' of the pituitary.

[22] In the cases of *group A*, in all of which pituitary destruction in some form was verified by autopsy or operation, failure to improve under treatment was not surprising in view of Smith's observation (22) that pituitary tissue never regenerates. This statement apparently did not take into account the hyperplasia of pregnancy, of castration or of the menopause.

close scrutiny shows no noteworthy difference in either the endocrine preparations used or the manner of their administration in the two groups. Therefore some of the improvement which undoubtedly took place may conceivably be ascribed to unintentional psychotherapy, to spontaneous resumption of pituitary activity or to coincidence. Yet, however conservative or skeptical one may be, a careful reading of many of the protocols forces one to believe that in some cases specific pituitary therapy must be given credit for the extraordinary improvement which occurred. The results with any one product were not consistent, but improvement from treatment occasionally seemed most convincing. In this connection one is reminded of the occasional benefits obtained by pancreatic therapy in the treatment of diabetes mellitus prior to the discovery of insulin.

However, failure to improve under treatment and even death do not establish a diagnosis of Simmonds' disease, as illustrated by the two striking cases published respectively by Richardson (129, *case* 3), and Osgood (130). Although they were typical of Simmonds' disease in symptomatology and in physical and laboratory findings, and the clinical courses ended in death, normal pituitary bodies were found at autopsy in both cases. Because of the normal pathological findings, Richardson considered his case as one of anorexia nervosa. Osgood called attention to the voracious appetite of his patient throughout most of the course of the disease. During a long period of hospitalization, she consumed 3000 calories daily although no diarrhea, fever or elevated basal metabolic rate which might account for her progressive emaciation occurred. This course would seem to exclude a diagnosis of anorexia nervosa, and the cause for the patient's emaciation and death remained a mystery.

Thus, again the question is raised whether severe disturbances of hormonic chemistry cannot occur in the absence of demonstrable histopathology. Bauer (429) inclined to such an interpretation as the explanation for Osgood's case; he believed that pituitary deficiency may exist without microscopic evidence. One does not hesitate to diagnose Cushing's disease or diabetes mellitus clinically, even though subsequent autopsy fails to reveal a lesion of the hypophysis, adrenals or islets of Langerhans.

ETIOLOGY, PATHOGENY, PATHOGENESIS

In 1910 Crowe, Cushing and Homans (437) reported the production of cachexia in puppies consequent to total (?) hypophysectomy. Emaciation developed within 3 weeks. In 1927 Smith (438) presented convincing experimental evidence that complete removal of the hypophysis in rats resulted in cachexia in the adults, in failure to grow in the young, in atrophy of the sex glands with loss of sexual function, in atrophy of the thyroid, parathyroid and adrenal cortex, in early senility, in general loss of tone and in splanchnomicria. These striking changes were noticeable 15 days after removal of the pituitary and reached their maximum 30 days after the operation. The damage could be rectified within a few days by daily pituitary transplants; thus growth was resumed and sexual function restored. Evans, Meyer, Pencharz and Simpson (439) were able to rectify the cachexia and to repair the adrenal damage of hypophysectomized rats by injections of their anterior-pituitary growth hormone. Houssay (440) found that hypophysectomy in dogs lowered the basal metabolic rate.

The status of these hypophysectomized animals simulates closely the clinical picture of Simmonds' disease. Deficiency of the growth-stimulating hormone would account for cachexia and splanchnomicria; lack of the gonadotropic hormones would seem responsible for amenorrhea, frigidity, impotence, atrophy of the genitalia, loss of sexual hair, and premature senility; insufficiency of the adrenotropic fraction could produce secondary atrophy of the adrenal cortex with consequent asthenia, hypotension, hypoglycemia, occasional pigmentation, some of the gastro-intestinal symptoms, and probably the lethal outcome; lack of thyrotropic hormone may be responsible for low basal metabolic rate, cold intolerance, dryness of the skin, bradycardia and hypothermia; lastly, lack of the diabetogenic or contrainsular hormone could be a factor in causing hypoglycemia.

Although we regard these interpretations as satisfactory and in agreement with modern experimental investigations, for the sake of completeness mention is made here of other conceptions. In 1926 Urechia and Elekes (315) questioned the pituitary origin of Simmonds' disease and stated that the primary seat of the disease was in the tuber cinereum. Accordingly they named the disease 'cachéxie tubérienne.'[23] Roussy and Mosinger (441) espoused a similar interpretation and stated definitely that cachectic states could result from lesions in the hypothalamus. The same conception was advocated by Mogilnitzky (174) and Marinesco and Parhon (187). Bailey and Bremer in 1922 (442) produced cachexia in two dogs and testicular degeneration in one of them by injury to the tuber cinereum; the pituitaries were later found to be normal microscopically.

[23] These authors noted that emaciation occasionally accompanies general paresis, catatonia, schizophrenia and tabes, and concluded therefore that severe weight loss might be of cerebral origin. They believed that the nodes in the tuber cinereum are sensitive to infections and intoxications, and can control temperature and tissue metabolism, and that lesions of these nodes might cause emaciation. They presented microscopic sections from cases of diabetes and general paresis showing infiltration around these nodes, and stated that in senile cachexia marked alterations occurred in the periventricular and supraopticus nuclei.

In recent years the interest in hypophyseal-hypothalamic interrelationships, which have been especially emphasized by Cushing (443), Fisher, Ingram and Ranson (444), and others, has increased. Kylin (132) suggested that a disturbance of any part of the 'pituitary-hypothalamus unit' might be responsible for Simmonds' disease. This reminds one of Biedl's hypothesis (referred to by Solis-Cohen and Weiss (445) as "seductive") that diabetes insipidus and dystrophia adiposogenitalis may be caused by: *a*), a lesion of the hypophysis producing deficient increations; *b*) a lesion obstructing the neural pathways to the hypothalamus and preventing the pituitary hormones from energizing the genito-trophic centers of the tuber cinereum; or *c*), normal secretion and normal pathways but disease of the hypothalamic centers which therefore would be unable to respond to the customary stimuli. This hypothesis straddles the pituitary stalk with one foot in the sella turcica and the other in the hypothalamus; it affords a platform broad enough for all parties to the controversy and seems almost too plausible to be true.

The conception of Falta (17, 133, 18, 19) as well as of Claude and Gougerot (14, 15, 16) that a simultaneous fibrosis involves several of the ductless glands seems untenable in the light of our present knowledge.

We have referred previously to perplexing cases, such as the one reported by Osgood (130), which were characteristic clinically but in which normal pituitaries were disclosed at autopsy. One is tempted to accept the suggestion of some writers that in these cases the pituitary is functionally rather than organically impaired and thus fails to stimulate the thyroid, sex and adrenal glands.

In many diseases, such as hyperthyroidism, adrenal cortical disease and Laurence-Moon-Biedl syndrome, the recognition of minor, abortive, atypical or partial 'formes fruste' has been considered proper, and such have also been described for Simmonds' disease. Zondek and Koehler (82) wrote of transient functional deficiency of the anterior lobe with moderate thinness. Von Bergmann (85) used the term, 'hypophyseal wasting (Magersucht)' to describe milder cases in which the pituitary might be intact but functionally deficient. He believed that the term, 'hypophyseal cachexia,' should be reserved for the fatal cases in which the pituitary was destroyed. Wahlberg (104) coined the eponym, 'asthenia gravis hypophyseogenea,' for mild, reversible cases. Schüpbach (276) referred to a mild functional form of the disease which improved under therapy, and a similar conception was introduced by Mainzer (353) under the expression, 'minor endocrinology,' as distinct from fully developed clinical pictures. Hicks (262) called the milder cases 'anterior pituitary dystrophy.'

Although theoretically one must concede that such partial or functional forms of the disease may occur, examination will disclose that they are usually found in young unmarried girls and are more likely instances of anorexia nervosa. However, Sheldon (446, 131) suggested pituitary abnormality as a factor in anorexia nervosa. He wrote of a pituitary 'blackout' of psychological origin on a background of endocrine infantility and termed this 'functional Simmonds' disease.' In his second paper he elaborated this hypothesis, and in emphasizing the almost exact parallelism clinically between true Simmonds' disease, anorexia nervosa and starvation, he hypothesized the existence of a similar central hypothalamic mechanism which inhibits anterior pituitary activity in all three conditions. The only differences he conceded were that in Simmonds' disease actual destruction of anterior pituitary cells takes place, in starvation an adjustment of the pituitary activity to a lowered level of existence occurs, and in anorexia nervosa a 'psychologic brake' is exerted on pituitary function. These ideas seem somewhat fanciful; and yet, we recognize the occurrence of acute exophthalmic goiter consequent to emotional shock, fright or grief, and of temporary suppression of the menses for similar reasons. Schur and Medvei (350) discussed the psychologic causation of endocrine dysfunction in 5 cases of anorexia nervosa.

The original conception of Gull that the disease known as anorexia nervosa arises from 'a morbid mental state' which manifests itself in a repulsion for food, has become traditional. As a result the other characteristics of the clinical picture develop. These include progressive loss of weight, weakness, amenorrhea and low basal metabolic rate. The amenorrhea is regarded as a more or less inevitable effect of starvation. In this connection one is reminded of the 'starvation amenorrhea' reported in central Europe during the war of 1914 to 1918. Sheldon (131) took issue with this conception, maintaining that "in between one-third and one-half of the cases" the amenorrhea "arises at either the same time as the anorexia or even before it, and cannot possibly be attributed to starvation." He introduced the term 'amenorrhea nervosa.'

It is equally disconcerting to account for the complete absence of any clinical evidence of deranged pituitary function in cases in which autopsy reveals destruction of the pituitary body. Several such cases are recorded in *group E*. Occasionally the neurosurgeon is called upon to remove a pituitary tumor in order to prevent blindness; and some of these patients exhibit no endocrine abnormalities. Why the same pathologic lesion produces glandular upheaval in one case and little or no sign of interference with

function in another remains a puzzle. Interesting in this connection is a strange case of Sheehan (386)—that of a woman who died during her twelfth pregnancy and in whom a shriveled, fibrotic pituitary was found at autopsy. Her extraordinary fertility and the lack of any evidence of Simmonds' disease are difficult to explain unless perhaps some aberrant hypophyseal tissue carried on normal pituitary function.[24]

Reference should be made here to six cases in *group F* (388, 155, 390, 78–79, 39, 393) in which the pituitaries were normal at autopsy but definite pathology was encountered in close proximity to the anterior lobe. Since all of these cases were typical clinically of Simmonds' disease, interference with the function of the adenohypophysis is conceivable although no cellular changes were found. Such a supposition seems tenable when one reflects on the intimate neural connections which link the hypophysis and hypothalamus (as previously discussed).

DIFFERENTIAL DIAGNOSIS

Since the outstanding characteristic of Simmonds' disease is marked loss of weight, one must first exclude the more customary causes of emaciation, such as tuberculosis,[25] severe hyperthyroidism, pellagra, sprue, and metastatic malignancy.[26] These conditions are readily differentiated as a lowered basal metabolic rate is not found in any of them. The natural shriveling of old age can hardly be confused with hypophyseal cachexia even though a subsequent autopsy may disclose visceromicria and generalized atrophy of the ductless glands including the pituitary (450).

Occasionally Addison's disease may present a problem in differential diagnosis as some of the patients with this primary adrenal disturbance are considerably underweight. However, the characteristic bronze pigmentation of adrenal cortical insufficiency is rarely seen in Simmonds' disease. Although some pigmentation has been noted occasionally, the characteristic spotting of the mucous membranes has never been reported in primary pituitary disease. Gastrointestinal complaints are far more pronounced and hypotension is likely to be more severe in Addison's disease. As a rule the basal metabolic rate is not as low in primary adrenal disease; hypogonadism, notably genital atrophy and loss of sexual hair,[27] is far more striking in Simmonds' disease. Finally, patients suffering from Simmonds' disease only occasionally derive benefit from adrenal cortical extract or high salt intake. Stephens (115), by using the salt excretion test of Cutler, Power and Wilder, has made possible the recognition of cases in which such a regime is helpful. He observed laboratory evidence of adrenal cortical insufficiency in six of his seven cases of hypopituitarism. When in rare cases differential diagnosis remains doubtful, recourse may be had to the trial of such a salt-poor regime for a few days, but only if the patient is under careful hospital supervision. A patient with Simmonds' disease is less likely to lapse into crisis under such conditions, the severity of the crisis depending upon the degree of secondary atrophy of the adrenal cortex.[28]

However, the truly difficult problem in differential diagnosis is the distinction between Simmonds' disease and anorexia nervosa. In addition to the reports already mentioned, this subject has been discussed recently by others (123, 413, 414, 415, 451–461). In spite of these contributions, the problem remains a difficult one. Therefore we have attempted to clarify it somewhat by statistical evaluation of the observations made in *group A* (verified typical Simmonds' disease) and those made in *group H* (anorexia nervosa). These comparisons follow. For the sake of clarity and emphasis they have been arranged in outline form.

[24] In this regard Melchionna and Moore (447) have recently recorded finding pituitary tissue in the pharynx in 51 of 54 consecutive autopsies at the New York Hospital.

[25] Heidkamp (448) reported the case of a boy aged 13 who died from widespread tuberculosis involving the cervical glands and the skin, with a cold abscess on the wall of the chest and pulmonary cavitation. Autopsy disclosed that a tuberculoma replaced the hypophysis. However, the emaciation seemed adequately accounted for by generalized tuberculosis especially as the other features of Simmonds' disease were absent. A similar case in a weak and emaciated 13-year-old girl was reported by E. Wagner (394). She had been scrofulous from her first year of life. Autopsy disclosed that her pituitary was largely replaced by tuberculous granulation tissue.

[26] In the older literature, syphilis, especially when it involves the central nervous system, is mentioned as a cause of cachexia. However, modern therapy has practically eliminated this condition. As examples of cachexia resulting in part at least from vomiting consequent to increased intracranial pressure, two cases reported by Kollarits (449) are cited. The two patients were females aged 17 and 28 (the latter sterile), who died as a result of primary sarcoma of the hypophysis. These two cases are not included in our tables because cachexia was the only symptom suggestive of Simmonds' disease.

[27] See case reported by Deusch (72), under the diagnosis, 'Addison's disease with pluriglandular insufficiency.'

[28] Aitken and Russell (336) reported the case of a waiter aged 50 years. The onset was acute and the patient was semiconscious for 3 days with a temperature of 105° F. The condition was explained subsequently by discovery of a sudden hemorrhage which had destroyed a chromophobe adenoma and practically the entire pituitary body. For the remaining 10 months of life the patient suffered from the effects of pituitary deficiency which in his case were: moderate wasting, great general weakness, a low systolic blood pressure of from 80 to 95 mm. Hg., a low level of blood sugar (fasting, 67 mg.% and not higher than 95 mg.% following 100 gm. glucose), and attacks of vomiting and prostration. These attacks and the hypotension, together with the marked asthenia, were suggestive of Addison's disease. At autopsy secondary atrophy of the suprarenals was found to be pronounced; there was, however, no Addisonian pigmentation. On the other hand, Ibotson (369) reported a case in which the patient was deeply pigmented but improved clinically on oral pituitary therapy.

REVIEW AND SUMMARY OF ANALYTICAL DATA FOR THE PURPOSE OF DISTINGUISHING BETWEEN SIMMONDS' DISEASE AND ANOREXIA NERVOSA

A striking similarity is noted in the incidence of three of the four cardinal characteristics:

1. *Cachexia*—65% and 75% respectively; *amount underweight*—average 21.2 and 20.7 kg. respectively; *amount of weight lost*—average 20.4 and 19.5 respectively.

2. *Loss of sexual function*—amenorrhea in 82% and 100% of the females respectively.

3. *Lowered basal metabolic rate*—average −33% and −29% respectively.

4. *Asthenia.* There is a definite difference in the frequency of occurrence of this symptom. It was noted in 90% of the cases in which Simmonds' disease was verified, but in only 55% of those recognized as cases of anorexia nervosa. However, this distinction is of doubtful differential value although it may be stated that the absence of asthenia in a young unmarried cachectic female would lead one to doubt the possibility of the diagnosis of Simmonds' disease.[29]

Other Items of Similarity

1. *Gastrointestinal disturbances* (excluding the symptom anorexia)—54% and 65% respectively.

2. *Bradycardia*—incidence of 21% and 31% respectively.

3. *Edema*—in 18% and 20% respectively.

4. *Blood pressure*—averages, 96/62 and 89/59 mm. Hg respectively.

Items Disclosing Significant Differences Between Simmonds' Disease and Anorexia Nervosa

1. *Onset post partum.* Onset soon after parturition, especially if delivery has been complicated by excessive hemorrhage and collapse, is strongly indicative of true Simmonds' disease. This inciting cause was never noted in the cases of anorexia nervosa but was recorded in 42% of the 65 verified female cases in *group A.*

2. *Onset following a severe infection.* This factor was mentioned only once in *group H.* However, it seems possible that a debilitating infection may predispose a neurotic individual to psychic anorexia.

3. *Alterations in the sella turcica.* Roentgen-ray evidence of a deformed sella turcica or calcification within it was noted in 43 per cent of the proved cases of Simmonds' disease, whereas no abnormalities in or about the sella were found in the cases of anorexia nervosa. This finding, therefore, in correlation with supporting clinical evidence, strongly suggests the diagnosis of Simmonds' disease.

4. *Reaction to treatment.* Marked improvement in response to treatment casts doubt on the presence of Simmonds' disease. This statement holds for the past and the immediate present, but may require considerable modification when anterior pituitary hormones become available which are comparable in potency and specificity to thyroid, insulin, parathormone, cortin, estradiol, and testosterone. In *group A* (verified Simmonds' disease) in which the mortality was 97 per cent, only 6 per cent of the patients were considered 'improved' or 'much improved' by any form of treatment. However, in the anorexia nervosa group 85 per cent could be so classified. A marked improvement after psychotherapy or a spontaneous return to complete health would strongly suggest the diagnosis of anorexia nervosa.

5. *Loss or absence of axillary and pubic hair (sexual hair).* This condition was far more common in verified Simmonds' disease than in anorexia nervosa—in 80 per cent as against 15 per cent.

6. *Premature senility.* This condition also may be considered as due to lack of gonadotropic hormone. It occurred far more frequently in the verified group than in *group H* (45% as against 5%).

7. *Atrophy of the breasts in females* occurred in 21 per cent of the cases in *group A* but not at all in *group H.*

8. *Pallor* was mentioned in 48 per cent of the cases in *group A* but not at all in *group H.* This difference is hard of explain as no marked differences were found in hemoglobin values or in red blood cell counts.

9. *Eosinophilia*—averages, 6.3% and 0.6% respectively.

Summary of Other Points of Interest

1. *Psychic abnormalities and anorexia.* As would be expected, mental-emotional disturbances and the symptom anorexia occurred more commonly in *group H,* namely in 95 per cent as compared to 64 per cent and 39 per cent in *group A.* Although their presence favors the diagnosis of anorexia nervosa, it by no means excludes the diagnosis of Simmonds' disease.

2. *Sex.* Females predominate in both groups, but the proportion of females is much higher in *group H* (9:1[30] as against 7:4 in *group A*).

3. *Average age.* The patients with true Simmonds' disease fall for the most part into the older decades

[29] That this is not invariably true was proved by the experience with one of our patients in whom the diagnosis of Simmonds' disease was verified at autopsy. The patient was a 17-year-old unmarried emaciated girl who developed terminal asthenia but who had played tennis a short time before her last entry into the hospital.

[30] Ryle (462) personally observed 51 patients with anorexia nervosa of which 46 were females and 5 were males, a ratio of 9:1.

(average 41 years as against 21 years in *group H*).[31]

4. *Duration of symptoms* was greater in the cases of true Simmonds' disease (average 7.9 years as against 2.8 years in anorexia nervosa).

Observations With Regard to Groups B and C

A survey of the statistical data for these groups (*group B*), cases typical clinically but without pathologic verification; *group C*, suggestive cases, some with pituitary pathology) reveals that the percentages of incidence of the various symptoms, signs and laboratory tests in general range between the extremes of *group A* and *group H*. This observation may be interpreted as suggesting that some of the cases in *groups B* and *C* are more likely to be instances of anorexia nervosa than of true Simmonds' disease. This is one of the reasons why only 20 cases of anorexia nervosa were selected for critical analysis, as we thought the number sufficient to indicate the general trend. Furthermore, comparison with the findings in Ryle's (462) group of 51 patients whom he observed personally, proves this to be the case.

CONCLUSIONS

1. An exhaustive search of the literature, correspondence with colleagues, and our personal experience, have yielded 595 cases with more or less suggestive evidence of Simmonds' disease. These cases have been subdivided into 7 groups and are presented in tabular form. With a few exceptions, each case report had been read in the original publication.

2. In 101 cases the diagnosis of Simmonds' disease was established both clinically and pathologically.

3. In 158 cases the clinical picture seemed typical, but the patients were either still living or autopsy had not been obtained. We are inclined to believe that many of these were cases of anorexia nervosa.

4. The cardinal features of clinical Simmonds' disease are *a*), marked loss of weight, often progressing to cachectic emaciation; *b*), loss of sexual function—amenorrhea in the female, loss of libido and potency in the male, and usually sterility in both sexes; *c*), a low basal metabolic rate. Asthenia is also a common symptom but does not seem to have as much diagnostic significance.

5. It should be relatively simple to eliminate advanced tuberculosis, malignant disease, and thyrotoxicosis as causes of cachexia as none of these conditions is associated with a low basal metabolic rate. Difficulty in differentiating Addison's disease from Simmonds' disease is rare.

6. The most difficult problem is the differentiation between true Simmonds' disease and anorexia nervosa. The occurrence of severe weight loss and a low basal metabolic rate in a young unmarried female who has never been pregnant favors the diagnosis of anorexia nervosa. Marked improvement or return to normal health as a result of psychotherapy or any other form of treatment available at present (endocrine therapy included), further suggests this diagnosis. A claim of cure in any case of true Simmonds' disease is open to doubt unless a pituitary tumor has been removed successfully.

The occurrence of severe weight loss, amenorrhea and a low basal metabolic rate in a woman over 30 years of age whose symptoms date from a postpartum hemorrhage and collapse, or whose sella turcica is deformed or contains calcification, and who in the course of the disease loses axillary and pubic hair, warrants a clinical diagnosis of Simmonds' disease.

Psychopathic disturbances favor the diagnosis of anorexia nervosa, but by no means exclude the possibility of the presence of true Simmonds' disease.

CASE SUMMARIES

The following case reports on 9 patients who were seen by us appear in the literature for the first time.

Case 1. L.P. (*group A*) (*University of California Clinic No. 48083*), was a male, aged 19, whose chief complaint was inability to gain weight. Onset had been gradual at the age of 13 years when he had been 155 cm. (5 ft. 1 in.) tall and had weighted 36.5 kg. (80 lb.). He had been somewhat weak since then, had noted occasional vertigo and headaches and his eyes had tired easily. He had had occasional erections but no libido. Two years before we saw him he had received 7 injections of anterior pituitary extract without definite effect. He had been drowsy frequently but had had no other psychic abnormalities.

On examination his height was 164 cm. (5 ft. 5 in.) and his weight 30.5 kg. (67 lb.) [as compared to an ideal weight of 56.7 kg. (125 lb.)]. He was emaciated and had eunuchoid skeletal proportions. There was a downy growth of beard on his face and lanugo hair on his back. The extremities were tapering and cyanotic. The genitalia were small and no prostatic tissue could be felt by rectum. Blood pressure was 92/60 in the supine position and fell to 70/50 on standing. Temperature was 35.2° C. (95.4° F.). Laboratory tests were as follows: B.M.R., −34%; blood hemoglobin, 74% (10.1 gm.) Sahli; red blood cells, 4,500,000 per cu. mm.; white blood cells, 15,000 per cu. mm. with 2% eosinophiles; urine, normal; Blood Wassermann and Kahn reactions negative; glucose tolerance—fasting 89 mg.%; ½ hr. 167 mg.%; 1 hr. 187 mg.%; 2 hr. 100 mg.%; 3 hr. 86 mg.%; 4 hr. 63mg .%; 5 hr. 75 mg.%; plasma chlorides (as NaCl), 597 mg.%; plasma cholesterol, 226

[31] Kylin (109, 110) attempted to establish a separate syndrome for adolescent cases of Simmonds' disease which he termed 'late pubertal emaciation.' We strongly suspect that many of these, especially those in which the patients responded remarkably to treatment, were actually instances of anorexia nervosa. Ryle (462) described a group of 33 cases of anorexia nervosa in young females from 15 to 29 years of age, the average age being 20 years.

mg.%; serum carotin, positive. Roentgenograms revealed that the bone age was 16 years and that the sella turcica was expanded and enlarged. The visual fields showed a temporal defect on the left.

The patient was operated upon by Dr. Howard Naffziger; an intrasellar Rathke's pouch cyst was drained and partially removed. Four months after operation no growth, appreciable weight-gain, or increase in sexual function had occurred and the B.M.R. had remained at −29%. However, vision had improved and general strength had somewhat increased. At this time testosterone propionate therapy was instituted. The doses of 25 mg. were given hypodermically 3 times weekly and were increased to 50 mg. 3 times weekly after 3 months and continued at that level for another 3 months. As a result the patient grew 1 inch in height, gained 19 pounds in weight and noted considerable increase in general strength. Sexual function appeared with frequent erections and occasional emissions, and the external genitalia approximately doubled in size. His voice became deeper, he began to shave occasionally, and the hair growth on the body increased. Also the visual fields showed improvement. During the early part of the treatment, transient ankle edema and mild diabetes insipidus (intake to approximately 5 quarts daily) were noted but cleared up spontaneously. Testosterone therapy was selected because of disappointing results in other cases of Simmonds' disease from the administration of anterior pituitary extracts and because we were eager to ascertain whether the maturity-provoking effects of testosterone would indirectly stimulate the spurt of growth which normally occurs at puberty.

Case 2. L.K., (*group B*) (*Office No. 2588*), a 61-year-old housewife, had been seen first at the age of 53 years at which time her chief complaint had been insomnia. She stated at that time that she had never been well since the birth of her second child when she was 31 years old. Since then she had had headaches, backaches and slowing of her mental processes. She frequently had felt depressed and had always been cold. She had had a tendency to anemia for which she had received periodic treatment with various tonics and with thyroid substance. Her skin and hair had become dry. Catamenia had ceased suddenly without menopausal symptoms when she was 34 years old. She had lost 18 pounds of weight in the preceding 3 years. Upon examination her height had been 59½ inches and her weight 118 lb. (ideal weight, 128 lb.). Her face had been slightly puffy and the eyebrows had been thin. The hair had been dry and scant in the axillary and pubic regions. Her tongue had been smooth and the nails brittle. Heart rate had been 66 per minute; blood pressure, 142/64. Laboratory tests had shown: hemoglobin, 73%; red blood cells, 3,820,000 per cu. mm. B.M.R. −27.7% Fluoroscopy of the chest had revealed no abnormalities. On an increased dose of thyroid and occasional iron and liver extracts, she had improved somewhat.

After 8 years she returned to us complaining of exhaustion and loss of weight. At this time she weighed 95 lb., her skin was pale, dry and wrinkled and her hair was dry and thin; her pulse rate was 50 per minute and her blood pressure 150/30. Glucose tolerance test results were as follows: fasting, 97 mg.%; ½ hr., 142 mg.%; 1 hr. 162 mg.%; 2 hr. 97 mg.%; 3 hr., 109 mg.%; 4 hr., 123 mg.%; 5 hr., 63 mg.%. The dose of thyroid was increased to 4 grains daily, but the patient's weight dropped to 94 lb. so that she was 42 lb. underweight. She was then hospitalized and insulin was administered, 5 U three times daily and then 10 U three times daily. As the latter dose caused reactions, it was reduced to 5 U twice daily. Anterior pituitary growth extract in 2 cc. doses 3 times weekly and later thyroid, 2 grains daily, were added. On this regime she improved somewhat and her weight gradually increased to 100 lb. She died 2 years later of sudden heart failure. No autopsy was performed.

Case 3. M.C., (*group B*) (*Office No. 6248*), a 31-year-old housewife, was first seen with complaints of loss of weight and asthenia. The onset had occurred 6 years before, 3 years after the birth of her only child, and had been accompanied by amenorrhea and loss of libido. Asthenia and some diminution of appetite had followed and within 5 years she had lost 62 lb. Two years before we saw her she had received thyroid substance and, for a short period, anterior pituitary extract injections and anterior pituitary substance orally, but no definite improvement had taken place. Other symptoms were: occasional frontal headaches, softening of the teeth, sensitivity to cold and some dryness of the skin and hair. She had become slow and negativistic.

The patient was 64¼ in. tall. She was extremely emaciated, weighing 64 lb. (70 lb. under ideal weight). The body temperature was 97° F. The heart rate varied between 44 and 53 beats per minute; blood pressure was 80–86/60. The breasts were small and the internal and external genitalia were atrophic. Some hypertrichosis was observed on the thighs and lower back. Laboratory investigation gave the following results: blood hemoglobin, 69% (Sahli); red blood cells, 3,310,000 per cu. mm.; white blood cells, 4,900 per cu. mm. with 1% eosinophiles; blood Kahn reaction, negative; B.M.R., −45%.

The patient did not cooperate in continuing either investigation or treatment.

Case 4. R.M., (*group C*) (*Office No. 5340*), a male newspaper worker aged 20, was first seen on Feb. 7, 1936, at which time his chief complaint was loss of hair. Onset had been 10 months before when he had sustained a fractured skull in an automobile accident. He had been unconscious for 5 weeks and now had a residual paralysis of the right side of the face, and an aneurism of the right internal carotid artery which caused a bulging of the right eye. He also had diabetes insipidus with an intake of 11 quarts of fluid daily. Other symptoms were daytime drowsiness, moderate anorexia, diminution of libido, moderate asthenia and loss of 33 pounds. He displayed no psychic changes other than those which would be expected as a result of a disfiguring accident. In the preceding 2 months he had lost considerable hair from legs and face.

The patient weighed 141 lb. (7 lb. underweight) and was 69 in. tall. In addition to the right facial paralysis he had exophthalmos on the right with diminished vision and pallor of the optic disc on that side. His skin was dry and somewhat pale. Hair was absent from the face, the extremities and axillary regions. The pubic hair was scant

and of feminine distribution. Heart sounds were regular, the rate being 72 per minute; blood pressure was 84/50. The genitalia were small. Laboratory tests showed: blood hemoglobin, 72%; red blood cells, 4,430,000 per cu. mm.; white blood cells 7,100 per cu. mm. with 3% eosinophiles, B.M.R. −17%; glucose tolerance test, fasting 77 mg.%; ½ hr., 135 mg.%; 1 hr. 102 mg.%; 2 hr., 58 mg.%; 3 hr., 78 mg.%; 4 hr., 53 mg.%; 5 hr., 58 mg.%.

Treatment with anterior pituitary growth extract was instituted and later pituitary gonadotropin was tried. On this regime the patient gained a little weight and had a slight increase in growth of hair. He was then given thyrotropic hormone without definite effect. On Nov. 16, 1936, Dr. Howard Fleming ligated the right common carotid artery. As a result moderate improvement of local symptoms in the head occurred, and after a period of 4 months the patient's weight and strength had increased slightly.

Case 5. V.D., (group C) (Office No. 5672), an 18-year-old girl, a student, was first seen on Nov. 24, 1936, complaining of asthenia, nervousness, palpitation, and inability to gain weight. Two years before she had noted that she tired easily and in the past year had lost 13 lb. Her menstrual periods had been regular until the last one which had been delayed 2 weeks. In the last year her teeth had become soft and she had had occasional frontal headaches. No psychic disturbances except the nervousness had occurred. On examination the patient appeared short and thin. Her height was 61 in. and her weight 89 lb. (26 lb. underweight). She looked rather young for her age. Moderate hypertrichosis was observed. The heart rate was regular at 90; blood pressure, 90/50. Laboratory tests showed: blood hemoglobin, 94%; red blood cells, 4,580,000 per cu. mm.; white blood cells, 5,600 per cu. mm. with 1% eosinophiles; B.M.R., −23.4%; urine and stool examinations, normal; glucose tolerance test, fasting, 85 mg.%; ½ hr., 115 mg.%; 1 hour., 102 mg.%; 2 hr., 83 mg.%; 3 hr. 80 mg.%; 4 hr., 89 mg.%; 5 hr., 57 mg.%. Treatment was instituted with adrenal cortical extract in doses of 1 cc. and later 2 cc. daily. After 1 month of this therapy her weight had dropped to 87¾ lb., whereupon she received anterior pituitary extract in doses of 1 cc. daily. As this treatment produced no definite effect, insulin therapy was instituted in gradually increasing doses. In 5 months she had gained to 97½ lb. and her general strength had improved, but her teeth were still poor and her menses irregular. She then received calcium and cod liver oil, and later insulin and estrogen therapy was resumed. Nevertheless, her condition remained practically unchanged.

Case 6. J.L., (group C) (Office No. 5860), was a 50-year-old unmarried male accountant who was first seen on May 13, 1937. complaining of blurring of vision and impotence. He had had mumps without complications at the age of 16. His last successful intercourse had occurred 2 years before and he had had occasional emissions since then. However, he had gradually lost libido and an attempted intercourse 2 weeks before had been unsuccessful. He had lost 27 lb. in the past 2 years, had developed some asthenia and had become moderately depressed. Vision in the left eye had gradually diminished for the past year. Examination showed him to be thin and pale with a cadaverous appearance. His height was 69 in., his weight, 115¾ lb. (51 lb. underweight). His skin was dry with some increase of pigmentation in the folds. His hair was dry but of normal thickness. He had bilateral cataracts. His heart beat was regular with a rate of 76; blood pressure was 90/68. The right testicle was considerably smaller than the left. Laboratory tests showed: blood hemoglobin, 68%; red blood cells, 3,640,000 per cu. mm.; white blood cells, 6,500 per cu. mm. with 2% eosinophiles; blood Kahn reaction, negative; B.M.R., +6.5%. A previous examination had revealed achlorhydria. Treatment with testosterone propionate injections 3 times weekly and dilute hydrochloric acid was begun. As no definite effects were noted, therapy with gonadotropic hormone 3 times weekly was instituted. After 4 weeks of this treatment his weight had dropped to 113½ lb. and he felt no better. Adrenal cortex extract injections 3 times weekly were then added to his regime, but he did not improve. His course was complicated by recurrent diarrhea.

Case 7. S.H., (group F) (Laguna Honda Home, University of California Service of Dr. LeRoy Briggs, *case No. 21567)*, was a Nicaraguan house-maid aged approximately 43 years. Nine months before we first saw her she had had tuberculous pleurisy with effusion and minimal tuberculosis of both lung apices. She had responded well to treatment at the San Francisco Hospital but as she had continued to be markedly asthenic and underweight, she had been referred to the Laguna Honda Home. She had had amenorrhea for 6 months.

The patient was emaciated. She weighed only 73½ lb. (59 lb. underweight) while her previous weight had been 127 lb. Her height was 60½ in. She was apathetic. The hair growth over her chin was increased. The skin, in addition to the racial pigmentation, showed a few spots of increased pigment over the face. Blood pressure was 100/60 and ranged as low as 86/54. Tenderness and spasm were elicited over the left lower quadrant of the abdomen. Laboratory tests showed the following: B.M.R., −29% (recheck, −31%); plasma chlorides, 510 mg.% (recheck, 573 mg.%); glucose tolerance test, fasting 77 mg.%; ½ hr., 143 mg.%; 1 hr., 187 mg.%; 2 hr., 139 mg.%; 3 hr., 83 mg.%; 4 hr., 44 mg.%; 5 hr., 52 mg.%; 6 hr., 93 mg.%. Roentgenograms of the chest showed old healed tuberculosis of the left apex and thickening of the pleura on the right; abdominal films showed no calcifications; the sella turcica was normal; gastrointestinal series showed an atonic stomach but no other abnormalities.

On a salt-free diet no Addisonian crisis occurred. As treatment with adrenal cortex extract and thyroid was ineffective, anterior pituitary extract was administered in doses of 1 cc. daily. After 4 months the patient's weight had gradually increased to 96 lb. At this time insulin was added to the regime and after another 4 months the patient's weight had increased to 107 lb. (a total gain of 33½ lb.); nevertheless she remained apathetic. Her menses had returned some time during the preceding 3 or 4 months. Her condition otherwise remained stationary under intermittent treatment with anterior pituitary extract, but the psychic symptoms became more marked and she

had occasional spells of disorientation at one time suggesting a catatonic schizophrenia. It became difficult to make her take food and her course started gradually downward in spite of treatment with benzedrine and later with a different preparation of anterior pituitary extract. She had occasional attacks of abdominal pain and nausea which could not be controlled by increased salt intake. About a year later her weight dropped to 85 lb. and she spent most of the time in bed. Cough and fever developed and tubercle bacilli were found in the sputum. After a short febrile course she died in coma.

Autopsy revealed extensive caseous tuberculosis of both lungs and tuberculosis of the ileum. The pituitary was normal in gross and microscopic appearance. The thyroid weighed 8.5 gm. and showed adenomata. The two adrenals weighed 9.5 gm. and showed moderate cortical hyperplasia and one small adenoma. The ovaries were fibrotic and the uterus was small.

Case 8. M.S., (group H) (Office No. 6357), was a girl, a student, aged 19 years and 4 months, who was first seen on Nov. 1, 1938, with a chief complaint of weakness. She had been overweight, reaching 160 lb. at the age of 12, and had been sensitive to taunts about being fat. She had dieted and lost weight to 130 lb. at the age of 14. She remained at this level until she was 16 years of age (3 years before we saw her) at which time she had a mild febrile illness following which she became asthenic and depressed. Her appetite diminished, she began to vomit after meals and had epigastric distress. Amenorrhea had developed suddenly with the onset of the illness. At that time her B.M.R. was recorded as −31% and her blood sugar as low.

Two years before we saw her, a diagnosis of Simmonds' disease had been made by a well-known internist in the Middle West and she had been treated for a time with anterior pituitary preparations. Only slight improvement had resulted. However, a series of chiropractic manipulations had been of considerable benefit and she had gained in weight from 89 to 115 lb. She had gradually lost some of this weight and her weakness had increase to the point at which she had to stop school. She had a compulsion to vomit after every meal and at times requested her mother to help her prevent this. At that time she was travelling about in search of a 'cure.' When we examined her she was thin and somewhat pale. Her height was 65 ⅜ in. and her weight 104 lb. (25 lb. underweight). Her skin was dry, her hair was coarse and rather scant in the axillary and pubic regions. Her breasts were small and the internal genitalia somewhat atrophic. Her pulse rate was 48 beats per minute and her blood pressure 78/40. Laboratory examinations revealed: hemoglobin, 68%; red blood cells, 3,190,000 per cu. mm.; white blood cells, 3,050 per cu. mm. with 2% eosinophiles; B.M.R., −19%. On a regime of forcing food, the patient gained 6 lb. in a week.

Case 9. M.A., (group H) (Office No. 5905), a school girl aged 16 years and 9 months, was first seen on June 18, 1935. Her chief complaints were irregular menses and inability to gain weight. She had had pleurisy with effusion at the age of 7. Menses had always been irregular since the menarche at 14 and she had had complete amenorrhea for 2 years. Her weight had been 127 lb. 1 year before we saw her and had dropped to 97 lb. 8 months before because she would not eat. On examination the patient was thin and had disproportionately long extremities. Her height was 64 in. and her weight 109¼ lb. (22 lb. underweight). She had a small adolescent goiter, and the pubic hair was scant. Blood pressure was 72/50. Laboratory tests showed: hemoglobin, 93% red blood cells, 5,190,000 per cu. mm.; eosinophiles, 1%; B.M.R., −5% and −14%. Roentgenograms of the gastrointestinal tract showed evidences of aerophagia. Further investigation revealed that she was deeply emotional and had been subjected to considerable 'nagging, at home; also, that she was feeling neglected socially. Home treatment was tried without any benefit and a year later we learned that the patient was in a mental hospital in a hypomanic state.

We express our appreciation to the following firms for liberal supplies of endocrine preparations used in the above cases: Ayerst, McKenna & Harrison, Ltd., Montreal, Canada; Parke, Davis & Co., Detroit, Michigan; E. R. Squibb & Sons, New York, N. Y.; Winthrop Chemical Co., Inc., New York, N. Y.

REFERENCES

1. Simmonds, M.: Ueber Hypophysisschwund mit tödlichem Ausgang. *Deutsche med. Wchnschr.* 40: 322. 1914.
2. Bostroem, A.: Atrophie des Hypophysisvorderlappens und hypophysäre Kachexie. *München med. Wchnschr.* 65: 441. 1918.
3. Simmonds, M.: Atrophie des Hypophysisvorderlappens und hypophysäre Kachexie. *München med. Wchnschr.* 65: 441. 1918.
4. Simmonds, M.: Atrophie des Hypophysisvorderlappens und hypophysäre Kachexie. *Deutsche med. Wchnschr.* 44:852. 1918.
5. Bostroem, A.: Beitrag zur klinischen Diagnose der Hypophysenschwundes. *Med. Klin.* 14: 690. 1918.
6. Leschke, E.: Beiträge zur klinischen Pathologie des Zwischenhirns. *Ztschr. f. klin. Med.* 87: 201. 1919.
7. Monakow, P. V.: in Discussion of paper by E. Leschke. *Verhandl. d. deutsch. Kong. f. innere Med.*, 34: 361. 1922.
8. Lichtwitz, L.: Drei Fälle von Simmondsschen Krankheit. *Klin. Wchnschr.* 1: 1877. 1922.
9. Ponfick, E.: Myxödem und Hypophysis. *Ztschr. f. klin. Med.* 38: 1. 1899.
10. Simpson, A. R.: Superinvolution of the uterus. *Edinburgh M. J.* 28: 961. 1883.
11. Hun, H., and T. M. Prudden: Myxoedema. Four cases with two autopsies. *Am. J. M. Sc.* (I) 96: 1. 1888; (II) 96: 140. 1888.
12. Stephens, L.: Case of anorexia nervosa; necropsy. *Lancet.* 1: 31. 1895.
13. Marshall, C. F.: A fatal case of anorexia nervosa. *Lancet* 1: 149. 1895.
14. Claude H., and H. Gougerot: Sur l'insuffisance simultanée de plusieurs glandes a sécrétion interne. *Compt. rend. Soc. de biol.* 63: 785. 1907; *J. de physiol. et de path. gén.* 10: 469. 1908.
15. Claude, H., and H. Gougerot: Les syndromes d'insuffisance pluriglandulaire. *Rev. de méd.*, Paris 28: 861. 1908.
16. Claude, H., and H. Gougerot: Les syndromes d'insuffisance pluriglandulaire. *Rev. de méd.*, Paris 28: 950. 1908.
17. Falta, W.: Die Erkrankungen der Blutdrüsen. Julius Springer Berlin, 1913.
18. Falta, W., and M. K. Meyers: Endocrine diseases. P. Blakiston's Son, and Co. Philadelphia, 1923.
19. Falta, W.: Die Simmondssche Krankheit. *Med. Klin.* 32: 1390. 1936.
20. Hirsch, S., and J. Berberich: Beitrag zur Frage der multiplen Blutdrüsensklerose. *Klin. Wchnschr.* 3:483. 1924.
21. Thür, W.: Über die Abgrenzung der Simmondsschen Kach-

exie von der multiplen Blutdrüsensklerose. *Frankfurt Ztschr. f. Path.* 36: 661. 1928.
22. Herrick, W. W.: The clinical features of hypophyseal cachexia (Simmonds' disease). Chapter XXXV, pp. 609–615, in "The Pituitary Gland." Williams and Wilkins Co., Baltimore, 1938. Publ. by Assoc. for Research in Nerv. and Mental Dis.
23. Meyler, L.: Simmonds' disease (hypophysary emaciation). *Acta Med. Scandinav.* 96: 157. 1938.
24. Petschacher, L., and H. Hönlinger: Über einen Fall von polyglandulärer Insuffizienz. *Med. Klin.* 18: 1462. 1922.
25. Zondek, H.: Ueber pluriglanduläre insuffizienz. *Deutsche med. Wchnschr.* 49: 339. 1923.
26. Stenström, T.: Einige Bemerkungen über spontanes hypoglykämisches Coma. *Deutsches Arch. f. klin. Med.* 152: 173. 1926.
27. Usadel, G.: Über pluriglanduläre Insuffizienz. *Frankfurt Ztschr. f. Path.* 44: 454. 1933.
28. Wachstein, M.: Über zwei mitt hyreotropem Hormon behandelte Fälle von Myxödem. *Klin. Wchnschr.* 13: 1434. 1934.
29. Lindemann, W.: Über Hypophysenvorderlappentherapie. *Zentralbl. f. Gynäk.* 62: 635. 1938.
30. Hochstetter, F.: Beitrag zur Klinik der multiplen Blutdrüsensklerose. *Med. Klin.* 18: 661. 1922.
31. Lindemann, E.: Über die multiple sogenannte Blutdrüsensklerose. *Virchows Arch. f. path. Anat.* 240: 11. 1922.
32. Falta, W.: Fall von multipler Blutdrüsensklerose. *Verhandl. d. deutsch. Kong. f. innere Med.* 35: 115. 1923.
33. Kivono, H.: Die Histopathologie der Hypophyse. *Virchows Arch. f. path. Anat.* 259: 388. 1926.
34. Dimmel, H.: Ein Fall von multipler Blutdrüsensklerose. *Wien. Arch. f. inn. Med.* 13: 377. 1927.
35. Lisser, H.: In Blumer's Bedside Diagnosis. W. B. Saunders Co., Philadelphia. vol. III, p. 431. 1928.
36. Richter, P. F.: Multiple Blutdrüsensklerose. *Deutsche med. Wchnschr.* 55: 1760. 1929.
37. Bingold, K.: Pluriglanduläre Insuffizienz. Blutdrüsensklerose. *München med. Wchnschr.* 78: 1587. 1931.
38. Liebers, M.: Ein Fall von klimakterischer Psychose mit multipler Blutdrüsensklerose bez. Atrophie. *Allg. Ztschr. f. Psychiat.* 97: 158. 1932.
39. Heinrichs, H.: Beitrag zur multiplen Blutdrüsensklerose (Falta). *Zentralbl. f. allg. Path.* 56: 52. 1932.
40. Umber, F.: Magerkeit und Magersucht. *Deutsche med. Wchnschr.* 60: 157. 1934.
41. Rössle, R.: Über wenig beachtete Formen der Entzündung von Parenchymen und ihre Beziehung zu Organsklerosen. *Verhandl. d. deutsch. path. Gesellsch.* 27: 152. 1934.
42. Boller, R., and A. Goedel: Zur Kenntnis der Klinik und pathologischen Anatomie der multiplen Blutdrüsensklerose. *Wien. Arch. f. inn. Med.* 27: 41. 1935.
43. Dunn, C. W.: Report of a case of "Simmonds' disease" (with recovery). *J. Nerv. & Ment. Dis.* 83: 166. 1936.
44. Oyamada, S., and T. Otomo: Ueber einen Fall von multipler Blütdrüsensklerose. *J. Orient. Med.* 24: 1173. 1936.
45. Meerwein, F.: Über die multiple Blutdrüsensklerose Falta. *Frankfurt Ztschr. f. Path.* 52: 54. 1938.
46. Priesel, A.: Pathologische Anatomie der Hypophyse. *Wien. klin. Wchnschr.* 51: 749. 1938.
47. Rand, C. W.: A case of supposed progeria (premature senility) in a girl of eight years. *Boston M. & S. J.* 171: 107. 1914.
48. Rumpel: Einen Fall von myxödemartiger Erkrankung bei Hodenatrophie vor. *Neurol. Centralbl.* 15: 428. 1896.
49. Sainton, P., and F. Rathery: Myxoedème et tumeur de l'hypophyse. *Bull. et mém. Soc. méd. d. hôp de Paris* 25: 647. 1908.
50. Eichhorst, H.: Über Veränderungen in der Hypophysis cerebri bei Kretinismus und Myxödem. *Deutsches Arch. f. klin. Med.* 124: 207. 1917.
51. Castleman, B., and S. Hertz: Pituitary fibrosis with myxedema. *Arch. Path.* 27: 69. 1939.
52. Poncin, and Goullioud: Myxoedème non operatoire. *Lyon méd.* 94: 126. 1900.
53. Djémil-Pacha: Un Cas de myxoedème opératoire survenu a la suite de l'extirpation des deux mamelles hypertrophiées chez un Homme. *Arch. internat. de chir.* 1: 81. 1903.
54. Gandy, C.: Myxoedème acquis de l'adulte avec régression sexuelle a l'état prépubère. Infantilisme réversiv de l'adulte. Dysthyroïdie et dysorchidie. *Bull. et mém. Soc. méd. d. hôp. de Paris.* 23: 1226. 1906.
55. Brissaud, H., and J. Bauer: Un cas d'infantilisme "Reversif" avec Autopsie. *Bull. et mém. Soc. méd. d. hôp. de Paris* 24: 39. 1907.
56. Brissaud, H. H., Gougerot and A. Gy: Insuffisance endocrinienne thyroïdotesticulaire. *Rev. Neurol.* 16: 1354. 1908.
57. Josserand, M.: A propos de l'infantilisme reversif. *Lyon méd.* 116: 75. 1911.
58. Gandy, C.: Nouveau cas d'infantilisme tardif de l'adulte. *Bull. et mém. Soc. méd. d. hôp. de Paris* 31: 837. 1911.
59. Gandy, C.: Infantilisme tardif de l'adulte. *Bull. méd., Paris* 25: 569. 1911.
60. Gougerot, H., and A. Gy: Insuffisance pluriglandulaire interne thyrotesticulo-surrénnale. *Nouvelle Icono. de la Saltpêtrière* 24: 449. 1911.
61. Fiessinger, N. and M. Sourdel: Insuffisance diastématospermatique acquise avec atrophie thyroïdienne. *Bull. et mém. Soc. méd. d. hôp. de Paris* 31: 861. 1911.
62. Faure-Beaulieu, M., M. Villaret and M. Sourdel: Syndrome pluriglandulaire. Étude clinique et anatomique d'un type a prédominance thyroïdienne et pancréatique. *Presse méd.* 19: 691. 1911.
63. Austregésilo, A., M. Pinheiro and E. Marques: Sur un cas de syndrome pluriglandulaire endocrinique. *Encéphale,* 8: 150. 1913.
64. Maresch, R.: Zur Kenntnis der polyglandulären Erkrankungen (Multiple Blutdrüsensklerose). *Verhandl. d. deutsch. path. Gesellsch.* 17: 212. 1914.
65. Hirsch, S.: Über eigentümliche Verlaufsformen polyglandulärer Syndrome, ihre Ätiologie und ihre pathologisch-anatomischen Grundlagen. *Deutsches Arch. f. klin. Med.* 140: 323. 1922.
66. Held, R.: Pluriglanduläre Insuffizienz. *Virchows Arch. f. path. Anat.* 261: 600. 1926.
67. Timme, W.: in Discussion of article by Frazier. *Arch. Neurol. & Psychiat.* 21: 18. 1929.
68. May, E., and F. Layani: La cachexie de croissance, syndrome pluriglandulaire avec participation pancreatique. Action favorable de l'insuline. *Bull. et mém. Soc. méd. des hôp. de Paris* 53: 302. 1929.
69. Weinstein, A.: Multiglandular syndromes resembling Simmonds' disease, with case report. *Am. J. M. Sc.* 189:245. 1935.
70. Good, W. H., and A. G. Ellis: A case of myxedema with tumor of pituitary body and lesions of other endocrine organs. *Endocrinology* 2: 431. 1918.
71. Engelbach, W., and J. L. Tierney: Diseases of the pituitary gland. I. Hypopituitarism. *Med. and Surg.* (St. Louis) 2: 466. 1918.
72. Deusch.: Addisonsche Krankheit mit pluriglandulärer Insuffizienz. *München med. Wchnschr.* 69: 373. 1922.
73. Zondek, H., and T. Reiter: Über das Wesen der Hormonwirkung. *Ztschr. f. klin. Med.* 99: 139. 1924.
74. Bernhardt, H.: Zur Frage der spezifisch-dynamischen Nahrungszufuhr bei endokrinen Erkrankungen. *Ztschr. f. klin. Med.* 99: 149. 1923.
75. Borchardt, L.: Die thyrosexuelle Insuffizienz, eine besondere Form der multiplen Blutdrüsensklerose. *Deutsche Arch. f. klin. Med.* 143: 35. 1923.
76. Falta, W.: Zwei Fälle von luetischer Kachexie. *Wien. klin. Wchnschr.* 38: 741. 1925.
77. Pettersson, A.: Ein Fall von spontanem hypoglykämischen Koma. *Acta Med. Scandinav.* 69: 232. 1928.
78. Oswald, A.: Die hypophysären Erkrankungen. *Schweiz. med. Wchnschr.* 9: 497. 1928.
79. Oswald, A.: Ueber Magersucht. *Schweiz. med. Wchnschr.* 16: 868. 1935.
80. Josefson, A.: Zerebrale Magersucht. *Acta med. Scandinav.* 75: 507. 1931.
81. Veil, W. H.: Die Klinik der Hypophysenkrankheiten. *München. med. Wchnschr.* 82: 58. 1935.
82. Zondek, H., and G. Koehler: Ueber zerebral-hypophysaere Magersucht. *Deutsche med. Wchnschr.* 54: 1955. 1928.
83. Zondek, H., and G. Koehler: Behandlung der hypophysär-

zerebralen Magersucht mit dem Hypophysenvorderlappenhormon Prolan. *Med. Klin.* 28: 1125. 1932.
84. CURSCHMANN, H.: Über Magersucht. *Ztschr. f. ärztl. Fortbild.* 26: 409. 1929.
85. VON BERGMANN, G.: Magerkeit und Magersucht (I). *Deutsche med. Wchnschr.* 60: 123. 1934.
86. VON BERGMANN, G.: Magerkeit und Magersucht (II). *Deutsche med. Wchnschr.* 60: 159, 1934.
87. VON BERGMANN, G.: Das Streben nach Synthese wissenschaftlicher Medizin und natürlicher Heilweisen. *Deutsche med. Wchnschr.* 64: 455. 1938.
88. SAUERBRUCH F.: Magerkeit und Magersucht. *Deutsche med. Wchnschr.* 60: 157. 1934.
89. BERNHARDT, H.: Magerkeit und Magersucht, *Deutsche med. Wchnschr.* 60: 158. 1934.
90. SEITZ, L.: Über hypophyse Störungen im Anschluss an Schwangerschaft und Geburt. *Monatschr. f. Geburtsh. u. Gynäk.* 99: 321. 1935.
91. VOGT, E.: Über die Behandlung der Magersucht und sekundären Amenorrhoe mit Implantation der Hypophyse eines Neugeborenen und mit Progynon und Proluton. *Med. Klin.* 31: 1393. 1935.
92. KNIPPING, H. W.: Über die Entstehung der Magersucht. *Deutsche med. Wchnschr.* 61: 1075. 1935.
93. KNIPPING, H. W.: Klinisches Bild und Therapie der Magersucht. *Deutsche med. Wchnschr.* 61: 1113. 1935.
94. KAUFMANN, C.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 932. 1936.
95. MEYER, W. C.: Untersuchungen und Beobachtungen an Fällen von hypophysärer Magersucht (Simmonds) und deren Behandlung, insbesondere durch Hypophysenimplantation. *Deutsche Arch. f. klin. Med.* 182: 351. 1938.
96. CURSCHMANN, H.: Über postpartuale Magersucht. *Monatschr. f. Geburtsh. u. Gynäk.* 86: 253. 1930.
97. LUCKE, H.: Hypophysäre Magersucht und Insulin. *Klin. Wchnschr.* 11: 1988. 1932.
98. ROTHMANN, H.: Diagnostik und Therapie der hypophysären Magersucht. *Acta med. Scandinav.* 87: 168. 1935.
99. STROEBE, F.: Die Bedeutung der hypophysären Magersucht für Ovarialfunktionsstörungen. *Zentralbl. f. Gynäk.* 59: 1156. 1935.
100. MENZEL, W.: Zur Behandlung der hypophysären Magersucht. *München med. Wchnschr.* 84: 969. 1937.
101. AZERAD, E.: Maigreur Hypophysaire: Forme Atténuée du Syndrome de Simmonds. Essai Therapeutique. *Rev. franç. d'endocrinol.* 15: 353. 1937.
102. KUNSTADTER, R. H.: Pituitary emaciation (von Bergmann). *Endocrinology* 22: 605. 1938.
103. BERBLINGER, W.: Zur Kenntnis der Simmondsschen Krankheit (Hypopituitarismus totalis). *Endokrinologie* 14: 369. 1934.
104. WAHLBERG, J.: Asthenia gravis hypophyseogenea. *Acta med. Scandinav.* 84: 550. 1935.
105. ASKANAZY, M., AND F. SCICLOUNOFF: Ueber das interrenoinsuläre Syndrom. Gibt es eine anscheinend primäre Polynesie (Inselreichtum) die zur tödlichen Kachexie führt?, *Schweiz. med. Wchnschr.* 16: 1046. 1935.
106. ROCH, M.: Polynesie, *Presse méd.* 45: 51. 1937.
107. WAHLBERG, J.: Hypophyseothyrogenic adiposity and emaciation. *J.A.M.A.* 106: 1968. 1936.
108. LABBE, M., R. BOULIN AND P. GOLDBERG: Syndrome hypophysothyro-génital. *Bull. et mém. Soc. méd. d. hôp. de Paris* 52: 1185. 1936.
109. KYLIN, E.: Senpubertär tvinsot. *Svenska läk-tidning* 33-Supplement: 1. 1936.
110. KYLIN, E.: Magersucht in der weiblichen Spätpubertat. *Deutsche Arch. f. klin. Med.* 180: 115. 1937.
111. KYLIN, E.: Die Behandlung der spätpubertären Magersucht, *Acta med. Scandinav.* 96: 75. 1938.
112. STROEBE, F.: Die Simmondssche Krankeit. Schlusswort. *Med. Klin.* 32: 1391. 1926.
113. WILTRAKIS, G. A., AND A. V. PARTIPILO: Non-myxedematous hypothyroidism. Case reported with psychosis. *Illinois M. J.* 74: 359. 1938.
114. STEPHENS, D. J.: Hypopituitarism. *Internat. Clin. I* (New Series 2): 97. 1939.
115. STEPHENS, D. J.: Chloride excretion in hypopituitarism with reference to adrenocortical function. *Am. J. M. Sc.* 199. 67. 1940.
116. ELSBERG, C. A., AND E. F. KRUG: A case of hypopituitarism with homonymous hemianopsia completely relieved by glandular treatment. *Arch. Ophth.* 46: 97. 1917.
117. GRAUBNER, W.: Die hypophysäre Kachexie (Simmondssche Krankheit). *Ztschr. f. klin. Med.* 101: 249. 1924–1925.
118. TAUBER, R. L.: Zur Kenntnis der Simmondsschen Krankheit. *Med. Klin.* 23: 1499. 1927.
119. CALDER, R. M.: Anterior Pituitary Insufficiency (Simmonds Disease). *Bull. Johns Hopkins Hosp.* 50: 87. 1932.
120. SILVER, S.: Simmonds' disease (cachexia hypophyseopriva). Report of case with post-mortem observations and review of literature. *Arch. Int. Med.* 51: 175. 1933.
121. HOWARD, C. P., AND L. J. RHEA: A case of Simmonds' disease due to a primary tumor of Rathke's pouch, observed over a period of twelve years. *Internat. Clin. I* (Series 46): 1. 1936.
122. ROBERT, P.: La Cachexie Hypophysaire et le problème de ses parentés morbides. Thèse de Paris, 1936.
123. VAN BALEN, G. F.: Anorexia nervosa und hypophysäre Magerkeit. *Acta med. Scandinav.* 101: 433. 1939.
124. SHEEHAN, H. L.: Simmonds' disease due to post-partum necrosis of the anterior pituitary. *Quart. J. Med.* 8: 277. 1939.
125. ESCAMILLA, R. F., AND H. LISSER: Simmonds' disease (hypophyseal cachexia). *California & West. Med.* 48: 343. 1938.
126. LISSER, H., AND R. F. ESCAMILLA: The clinical diagnosis of Simmonds' disease (Hypophyseal Cachexia), *Tr. A. Am. Physicians* 53: 210. 1938.
127. GREENE, J. A.: Diagnosis and treatment of Simmonds' disease. *J. Iowa M. Soc.* 27: 6. 1937.
128. RICHARDSON, H. B.: Simmonds' disease and anorexia nervosa. *Tr. A. Am. Physicians* 52: 141. 1937.
129. RICHARDSON, H. B.: Simmonds' disease and anorexia nervosa. *Arch. Int. Med.* 63: 1. 1939.
130. OSGOOD, E. E.: Pituitary cachexia? *Endocrinology* 23: 656. 1938.
131. SHELDON, J. H.: Discussion on anorexia nervosa. *Proc. Roy. Soc. Med.* 32: 738. 1939.
132. KYLIN, E.: Die Simmondssche Krankheit. *Ergebn. d. inn. Med. u. Kinderh.* 49: 1. 1935.
133. FALTA, W., AND M. K. MYERS: The ductless glandular diseases. P. Blakiston's Son & Co. Philadelphia, 1916.
134. SIMMONDS, M.: Ueber embolische Prozesse in der Hypophysis. *Virchow's Arch. f. path. Anat.* 217: 226. 1914.
135. MARESCH, R.: Fall von polyglandulärer Erkrankung. *Zentralbl. f. allg. Path.* 25: 402. 1914.
136. SIMMONDS, M.: Ueber Kachexie hypophysären Ursprungs. *Deutsche med. Wchnschr.* 42: 190. 1916.
137. SIMMONDS, M.: Kachexie hypophysären Ursprungs *Med Klin.* 12: 655. 1916.
138. SCHLAGENHAUFER, O.: Zur Kachexie hypophysären Ursprungs, *Virchow's Arch. f. path. Anat.* 222: 249. 1916.
139. FRAENKEL, E.: Demonstration von Präparaten eines Falls von hypophysärer Kachexie. *Neurol. Zentralbl.* 35: 778. 1916.
140. FRAENKEL, E.: Präparate von hypophysärer Kachexie. *Deutsche med. Wchnschr.* 42: 1369. 1916.
141. BOSTROEM, A.: Atrophie des Hypophysisvorderlappens und hypophysäre Kachexie. *Deutsche med. Wchnschr.* 44: 871. 1918.
142. BUDDE, M.: Zur Kenntnis der bösartigen Hypophysengeschwülste und hypophysären Kachexie. *Frankfurt Ztschr. f. Path.* 25: 16. 1921.
143. REYE, E.: Zur Klinik und Therapie der "Kach hypophysären Ursprungs." *Deutsche Ztschr. f. Nervenh.* 68–69: 153. 1921.
144. REYE, E.: Das klinische Bild der Simmondsschen Krankheit in ihrem Anfangsstadium und ihre Behandlung., *München med. Wchnschr.* 73: 902. 1926.
145. KAMINSKI, J.: Zur Frage der Entstehung der Simmondsschen Krankheit. *Frankfurt Ztschr. f. Path.* 45: 290. 1933.
146. VON MONAKOW, P.: Zur Pathologie der Hypophyse. *Schweiz Arch. f. Neurol. u. Psychiat.* 8: 200. 1921.
147. BÜCHLER, P.: Beiträge zu den Hypophysenveränderungen. *Ztschr. f. d. ges. Neurol. u. Psychiat.* 72: 207. 1921.

148. Veit, B.: Ein Beitrag zur pathologischen Anatomie der Hypophyse. *Frankfurt Ztschr. f. Path.* 28: 1. 1922.
149. Simons, A.: Hypophysäre Kachexie. *Zentralbl. f. d. ges. Neurol. u. Psychiat.* 30: 125. 1922.
150. Simons, A.: Fall von Kachexia hypophysecopriva. *Klin. Wchnschr.* 1: 2017. 1922.
151. Simons, A.: Hypophysäre Kachexia. *Deutsche med. Wchnschr.* 48: 1397. 1922.
152. Simons, A.: Hypophysäre Kachexie. *Zentralbl. f. d. ges Neurol. u. Psychiat.* 39: 191. 1925.
153. Pribram, B. D.: In discussion of article by E. Leschke. *Verhandl. d. deutsch. Kong. f. innere Med.* 34: 355. 1922.
154. Plaut, R.: Gaswechseluntersuchungen bei Fettsucht und Hypophysiserkrankungen. *Deutsches Arch. f. klin. Med.* 139: 285. 1922.
155. Jaffe, R.: Luetische Erkrankunen der Hypophyse. *Frankfurt Ztschr. f. Path.* 27: 324. 1922.
156. Zondek, H.: Kachexia Hypophysiopriva. *Klin. Wchnschr.* 1: 1385. 1922.
157. Zondek, H.: Die Krankheiten der Endokrinen Drüsen. Julius Springer, Berlin, 1926.
158. Zondek, H., and C. Krausnitz: The diseases of the endocrine glands. William Wood & Co., Baltimore, 1935.
159. Jungmann, P.: Über eine isolierte Störung des Salzstoffwechsels, *Klin. Wchnschr.* 1: 1546. 1922.
160. Knoll, W.: Beitrag zum Bilde der hypophysären Kachexie. *Wien. Arch. f. inn. Med.* 4: 555. 1922.
161. Keilmann, K.: Ueber eine grosse Hypophysenzyste mit hypophysärer Kachexie. *Zentralbl. f. allg. Path. u. path. Anat.* 33: 113. 1922.
162. Jungmann, P.: Zur Pathologie des Salzstoffwechsels. *Klin. Wchnschr.* 2: 18. 1923.
163. Buday, K.: Über die hypophysäre Kachexia. *Klin. Wchnschr.* 2: 902. 1923.
164. Jakob, A.: Discussion. *Deutsche med. Wchnschr.* 49: 735. 1923.
165. Jakob, A.: Zwei Fälle von Simmondsscher Krankheit mit besonderer Berücksichtigung der Veränderungen im Zentralnervensystem. *Virchows Arch. f. path. Anat.* 246: 151. 1923.
166. von Grabe, E.: Einen Fall von hypophysärer Kachexie. *Deutsche med. Wchnschr.* 49: 735. 1923.
167. Jedlicka, V.: Syphilitic pituitary cachexia, abs. *J.A.M.A.* 81: 2072. 1923 (orig., Casopis lekaruv ceskych Prague 62: 1027. 1923).
168. Schereschewskij, N.: Zur Symptomatologie und Diagnostik der Simmondsschen Krankheit. *Zentralbl. f. d. ges. Neurol. u. Psychiat.* 42: 434. 1926.
169. Schereschewsky, A.: La symptomatologie et la diagnostic de la maladie de Simmonds (Cachexie hypophysaire). *Rev. franç. d'endocrinol.* 5: 275. 1927.
170. Pribam, B. O.: Zur Frage des Alterns. *Virchows Arch. f. path. Anat.* 264: 498. 1927.
171. Reiche, F.: Zum Kapitel der hypophysären Kachexie. *Med. Klin.* 23: 1569. 1927.
172. Pennetti, G.: Sindromi ipofisarie malattia del Simmond e coma pituitario del miermet. *Riforma med.* 44: 9. 1928.
173. Altman, F.: Über einen Fall von hypophysärer Kachexia. *Frankfurt Ztschr. f. Path.* 36: 393. 1928.
174. Mogilnitzky, B. N.: Zur Frage der Entstehung der hypophysär subthalamischen Syndrome. *Virchows Arch. f. path. Anat.* 269: 1. 1928.
175. Meng, H.: Über Wucherung der Neurohypophyse bei Simmondsscher Erkrankung. *Frankfurt Ztschr. f. Path.* 36: 650. 1928.
176. Omelskyj, E.: Zur Nebennierenpathologie. Über cytotoxische Schrumpfnebenniere bei hypophysärer Kachexie und über ortliche Schrumpfnebenniere. *Virchows Arch. f. path. Anat.* 271: 377. 1929.
177. Good, T. S., and K. O. Newman: Pituitary cachexia in a case of tabes dorsalis. *Lancet* 1: 765. 1929.
178. Mertz, W.: Beitrag zur Frage der Entstehung der hypophysären Kachexie. *Frankfurt Ztschr. f. Path.* 40: 452. 1930.
179. Reiche, F.: Zur Kenntnis der Simmondsschen Krankheit. *Med. Klin.* 26: 1447. 1930.
180. Strauss, I., and J. H. Globus: Simmonds' Disease: Fatal Issue; Necropsy Findings. *J. Nerv. & Ment. Dis.* 72: 566. 1930.
181. Bostroem, A.: Hypophysäre Kachexie bei Hirnarteriosklerose. *Deutsche Ztschr. f. Nerven.* 117: 27. 1931.
182. Farquharson, R. F., and D. Graham: Cases of Simmonds' disease. *Tr. A. Am. Physicians* 46: 150. 1931 (abs., *J.A.M.A.* 96: 1987. 1931).
183. Farquharson, R. F., T. H. Belt and G. L. Duff: Simmonds' disease. Clinical and pathological observations in four cases. *Tr. Am. Clin. and Climat. Assoc.* 54: 106. 1938.
184. Reye, E.: Klinik und Therapie der Simmonds'schen Krankheit und verwandter Zustände. *Zentralbl. f. inn. Med.* 52: 946. 1931.
185. Schürmann: Magerkeit und Magersucht. *Deutsche med. Wchnschr.* 60: 157. 1934.
186. Schob and Güntz: Alzheimersche Krankheit kombiniert mit Simmondsscher Erkrankung (Hypophysäre Kachexie). *Allg. Ztschr. f. Psychiat.* 97: 242. 1932.
187. Marinesco, G., and C. I. Parhon: Sur un cas de diabète insipide avec cachexie hypophysaire, infantilisme, sénilisme, atrophie des organes génitaux et convulsions de type epileptique. *Rev. franç. d'endocrinol.* 10: 105. 1932.
188. Riecker, H. H., and A. C. Curtis: Hypophyseal cachexia (Simmonds' disease). *J.A.M.A.* 99: 110. 1932.
189. Cushing, H.: Dyspituitarism twenty years later. *Arch. Int. Med.* 51: 487. 1933.
190. Fink, E. B.: Gumma of the hypophysis and hypothalamus *Arch. Path.* 15: 631. 1933.
191. Hoet, M.: La maladie de Simmonds et ses rapports avec l'hormone thyréotrope de l'hypophyse. *Bull. Acad. roy. de méd. de Belgique* 13: 445. 1933.
192. Pappenheim, M.: Welches Krankheitsbild bietet die hypophysäre Kachexie. *Wien. klin. Wchnschr.* 47: 148. 1934.
193. Hantschmann, L.: Beitrag zu den Stoffwechselstörungen bei Hypophysenvorderlappenausfall. *Deutsche Arch. f. klin. Med.* 176: 397. 1934.
194. Hantschmann, L.: Ödeme bei Eiweissmangel. *Deutsche med. Wchnschr.* 64: 361. 1938.
195. Bratton, A. B., and A. B. Field: A case of Simmonds' disease. *Lancet* 2: 806. 1934.
196. Kylin, E.: Två fall av Simmonds sjukdom, behandlade med hypofystransplantation, *Svenska läk. tidning* 32: 908. 1935.
197. Kylin, E.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 933. 1936.
198. Kylin, E.: Ergebnisse von 24 Hypophysentransplantationen. *Klin. Wchnschr.* 15: 1756. 1936.
199. Gunther, L., and C. B. Courville: Hypophyseal cachexia (Simmond's disease) with atrophy of the anterior lobe of the pituitary gland. *J. Nerv. & Ment. Dis.* 82: 40. 1935.
200. Rose, E., and G. Weinstein: Cachexia hypophyseopriva (Simmond's disease) with thyroid and suprarenal insufficiency. *Endocrinology* 20: 149. 1936.
201. Boom, H.: Hypophysaire cachexie van Simmonds met skeletafwizkingen, *Nederl. tijdschr. v. geneesk.* 80: 3336. 1936.
202. Boom, H., and J. W. Boehmer: Hypophysaire cachexie van Simmonds, ostitis deformans van Paget en gewrichts a fwijkingen. *Nederl. tijdschr. v. geneesk.* 82: 5731. 1938.
203. Stewart, A.: A case of Simmonds' disease, *Lancet* 2: 1391. 1936.
204. Hubschmann, H.: Versagen der Zuckerregulation, *München med. Wchnschr.* 84: 697. 1937.
205. Gallavan, M., and A. T. Steegmann: Simmonds' disease (anterior hypophyseal insufficiency), *Arch. Int. Med.* 59: 865. 1937.
206. Weiner, H. A.: Simmonds' disease: Report of a case, *Yale J. Biol. & Med.* 10: 31. 1937.
207. De Martel, T., and J. Guillaume: Kyste hypophysaire choléstéatomateux chez un enfant présentant un syndrome de Simmonds. Opération. Amélioration considérable du syndrome. *Rev. neurol.* 69: 384. 1938.
208. Davis, M. A., and B. Postle: Hypophyseal cachexia (Simmonds' disease). *Ohio State M. J.* 34: 879. 1938.
209. Plummer, D. E., and J. R. Jaeger: Pituitary cachexia (Simmonds' disease), *Arch. Neurol. & Psychiat.* 40: 1013. 1938.
210. Lichtenfeld, C.: Über zwei Fälle von Simmonds'scher Kachexie, *Zentralbl. f. inn. Med.* 59: 913. (II) 59: 930. 1938.

211. Altschule, M. D.: from Beth Israel Hospital, Boston, Massachusetts. Personal communication.
212. Leake, W., and W. Beckett: From Los Angeles County Hospital, Los Angeles, California. Personal communication.
213. Bergstrand, H.: Ein Obduktionsfall von Morbus Simmond. *Acta chir. Scandinav.* 82: 227. 1939.
214. Urechia, C., and A. Retezeanu: Maladie de Simmonds avec contrôle anatomique. *Bull. et mém. Soc. méd. d. hôp. de Paris* 55: 698. 1939.
215. Seeger, E.: Akute hypophysäre Insuffizienz nach Appendektomie. *München med. Wchnschr.* 86: 882. 1939.
216. Hart, J. F., and J. R. Lisa: Pituitary cachexia: Report of a case. *Endocrinology* 25: 130. 1939.
217. Foley, M. P., A. M. Snell and W. McK. Craig: Anterior pituitary tumor associated with cachexia, hypoglycemia and duodenal ulcer. *Am. J. M. Sc.* 198: 1. 1939.
218. Reye, E.: Hypophysäre Kachexie. *München med. Wchnschr.* 67: 1302. 1920.
219. Reye, E.: Über hypophysäre Kachexie auf Basis von Lues acquisita mit Ausgang in Heilung. *Med. Klin.* 16: 1313.1920.
220. Schneider, H.: Kachexie bei wahrscheinlich fortgeleiteter Hypophysentuberkulose. *Wien. med. Wchnschr.* 72: 233. 1922.
221. Schneider, H.: Kachexie bei wahrscheinlich fortgeleiteter hypophysentuberkulose. *Klin. Wchnschr.* 1: 1027. 1922.
222. Lichtwitz, L.: Simmondsscher Krankheit. *München med Wchnschr.* 69: 138. 1922.
223. Lichtwitz, L.: Ein Fall Simmondsscher Krankheit. *Klin. Wchnschr.* 1: 397. 1922.
224. Lichtwitz, L.: Hypophysärer Kachexie. *Deutsche med. Wchnschr.* 48: 508. 1922.
225. Bauer, J.: Innere Sekretion. Julius Springer, Berlin, 1927.
226. di Guglielmo, G.: Contributo alla conosciza della cachessia ipofisaria (malattia di Simmonds), *Boll. d. Soc. med.-chir., Pavia* 2: 167. 1927.
227. Cushing, H.: Acromegaly from a surgical standpoint. *Brit. M. J.* 2: 1. 1927.
228. Mason, E. H.: Abnormal specific dynamic action of protein, glucose and fat associated with undernutrition. *J. Clin. Investigation* 3: 353. 1927.
229. Herman, K.: Über die Simmondssche Krankheit. *Klin. Wchnschr.* 7: 944. 1928.
230. Herman, C.: LaMaladie de Simmonds. *Rev. franç. d'endocrinol.* 6: 301. 1928.
231. Frazier, C. H.: Pituitary cachexia. *Arch. Neurol. & Psych.* 21: 1. 1929.
232. Colden, C.: Simmonds'sche Krankheit (Dystrophia cachectico-genitalis) mit Augenbefunden. *Klin. Monatsbl. f. Augenh.* 82: 769. 1929.
233. DeRudder, B.: Simmondssche hypophysäre Kachexie im Kindesalter. *Ztschr. f. Kinderh.* 50: 113. 1930.
234. Stocks, J. W.: A case of pituitary cachexia. *Lancet* 2: 349. 1930.
235. Constantini, F.: Contributo clinico alla conoscenza della malattia di Simmonds (cachessia ipofisaria). *Policlinico (sez. med.)* 38: 251. 1931.
236. Nielsen, O.: Simmonds' sygdrom, *Hospitalstid.* 74: 781. 1931.
237. Kylin, E.: Ett fall av Simmonds sjukdom. *Svenska läk.-tidning* 28: 1086. 1931.
238. Calder, R. M.: Pituitary cachexia (Simmonds' disease) treated with anterior pituitary extract. *J.A.M.A.* 98: 314. 1932.
239. Ehrhardt, K.: Klinische und tierexperimentelle Untersuchungen über Hormone des Hypophysenvorderlappens. *Arch. f. Gynäk.* 148: 235. 1932.
240. Ehrhardt, K., and C. Kittel: Zur Behandlung hypophysärer Störungen durch Hypophysenimplantation. *Ztschr. f. klin. Med.* 132: 246. 1937 (abs. *Zentralbl. f. inn. Med.* 59: 600. 1938).
241. Lucacer, M.: Sindrome di Simmonds con esito in guarigione. *Riforma med.* 48: 547. 1932.
242. Kissling, K.: Ueber hypophysäre Kachexie. *München med. Wchnschr.* 79: 655. 1932.
243. Kylin, E.: Ett relativt tidigt fall av Simmonds sjukdom. *Svenska läk.-tidning* 29: 609. 1932.
244. Steinitz, E., and E. Thau: Über hypophysäre Kachexie. *Therap. d. Gegenw.* 73: 296. 1932.
245. Hurthle, R.: Über hypophysäre Kachexie. *Med. Klin.* 28: 1637. 1932.
246. Brougher, J. C.: Pituitary cachexia. Report of a patient treated with anterior pituitary extract. *Endocrinology* 17: 128. 1933.
247. Kylin, E.: Ett nytt fall av Simmonds sjukdom. *Svenska läk.-tidning.* 30: 393. 1933.
248. Belaiche, M.: Contribution à l'étude de la cachexie de Simmonds. Thèse de Paris. 1933.
249. Barker, L. F.: A case of hypophyseal dwarfism probably due to cyst or benign neoplasm originating in residues of the ductus craniopharyngius. *Endocrinology* 17: 647. 1933.
250. Cervera, L., A. Folch and B. Benaiges: Considérations sur un cas de maladie de Simmonds, *Rev. franç. d'endocrinol.* 12: 15. 1934.
251. Hotop F.: Simmondsscher Krankheit. *Klin. Wchnschr.* 13: 1102. 1934.
252. Hotop, F.: Simmondsscher Krankheit. *München. Med. Wchnschr.* 81: 963. 1934.
253. Selander, P.: Ett fall av Simmonds sjukdom. *Hygiea* 96. 125. 1934.
254. Richtzehain, W.: Die Behandlung psychischer Störungen mit Organ- und Hormonpräparaten, *Therap. d. Gegenw.* 75: 302. 1934.
255. Herman, K.: Neuere Erfahrungen mit der Simmondsschen Krankheit. *München med. Wchnschr.* 81: 1460. 1934.
256. Herman, K.: New observations in Simmonds' disease. *J.A.M.A.* 103: 1743. 1934.
257. Herman, K.: New experiences with Simmonds' disease. *Am. J. Digest. Dis. & Nutrition* 3: 382. 1936.
258. Kylin, E.: Ytterligare några lyckade fall av hypophystransplantation vid Simmonds' sjukdom. *Svenska läk.-tidning* 33: 385. 1936.
259. Monterumici, D. M.: LaSindrome di Simmonds e la sua cura, *Terapia* 25: 46. 1935.
260. Lederer, J. A.: L'hormone thyréotrope et le metabolisme de base dans les syndromes hypophysaire. *Rev. belge sc. méd.* 7: 369. 1935.
261. Hicks, C. S., and F. S. Hone: Pituitary cachexia with disturbance of circulatory regulation. Result of treatment with prolan. *Proc. Roy. Soc. Med.* 28: 925. 1935.
262. Hicks, C. S.: Disorders of the pituitary gland in relation to metabolic and circulatory disturbance. *M. J. Australia* 1: 441. 1938.
263. Hawkinson, L. F.: Simmonds' disease (Pituitary cachexia). Report of a case in which the patient responded to anterior pituitary-like principle of pregnancy urine. *J.A.M.A.* 105: 20. 1935.
264. Shaw, M.: Simmonds' disease (Pituitary cachexia). *Proc. Roy. Soc. Med.* 28: 1176. 1935.
265. Langmead, F. S.: in Discussion of article by Shaw *Proc. Roy. Soc. Med.* 28: 1177. 1935.
266. Aldrich, C. A., and J. A. Walsh: Cachexia hypophysiopriva (Simmond's disease). Report of a case in an adolescent girl. *J. Pediat.* 7: 491. 1935.
267. Kylin, E.: Om behandling med rê binjure. *Svenska läk.-tidning.* 32: 1802. 1935.
268. Moehlig, R. C.: Pituitary cachexia (Simmonds' disease). *Endocrinology* 20: 155. 1936.
269. Bulger, H. A., D. P. Barr: Metabolic studies of pituitary insufficiency. *Endocrinology* 20: 137. 1936.
270. Reiss, M.: Ziekte van Symmonds. *Nederl. tijdschr. v. geneesk.* 80: 1773. 1936.
271. Kylin, E.: Ytterligare några fall av Simmonds sjukdom, med framgång behandlade med hypophystransplantation. *Svenska läk-tidning* 33: 1009. 1936.
272. Schoo, A. G.: Hypophysaire cachexia. *Nederl. tijdschr. v. geneesk.* 80: 4581. 1936.
273. De Gennes, L.: Cachexie hypophysaire. *Bull. et mém. Soc. méd. d. hôp. de Paris* 52: 1519. 1936.
274. Azérad, E.: in Discussion of article by De Gennes. *Bull. et mém. Soc. méd. d. hôp. de Paris* 52: 1524. 1936.
275. Cahane, M., and T. Cahane: Sur un cas de mélancolie associé a un syndrome fruste de Simmonds. *Ann. méd.-psychol.* 94: 798. 1936.

276. Schüpbach, A.: Zur Hormonbehandlung der Simmonds' schen Krankheit und verwandter asthenischer Zustände. *Schweiz. med. Wchnschr.* 66: 1245. 1936. (abs. *J.A.M.A.* 108: 339. 1937).
277. Kraus, F., and O. H. Müller: Über schwere Hypophysenvorderlappeninsuffizienz und ihre Behandlung. *Klin. Wchnschr.* 16: 118. 1937.
278. Van Rijsewijk, C.: Een Geval van de Ziekte van Simmonds. *Nederl. tijdschr. v. geneesk.* 81: 32. 1937.
279. Ravenel, S. F.: Anterior pituitary insufficiency (Simmonds' disease). *South. M. J.* 30: 403. 1937.
280. De Langen, C. D.: Het Samengaan van de Ziekte van Simmonds met die van Gee-Thaysen. *Nederl. tijdschr. v. geneesk.* 81: 2896. 1937. (abs. *J.A.M.A.* 109: 398. 1937).
281. Regester, R. P., and T. D. Cuttle: Cachexia hypophyseopriva (Simmonds' disease). *Endocrinology* 21: 558. 1937.
282. Reuter, A., and I. Lamprecht: Zur Klinik der suprasellären Tumore, *Deutsche med. Wchnschr.* 63: 1033. 1937.
283. Van Melle, M. M., and H. K. Hartman: Een Geval van Magerheid, berustend op afwijkende Hypophysewerking. *Nederl. tijdschr. v. geneesk.* 82: 1720. 1938.
284. Jutoran, M.: Sindrome de Simmonds o caquexia hipofisaria. *Semana méd.* 45: 1180. 1938.
285. Van Bogaert, L.: Sur l'hypopituitarisme avec myélose funiculaire. (pseudo-tabes acromegalique de Sternberg, pseudo-tabes hypophysaire d'Oppenheim). *Bull. et mém. Soc. méd. d. hôp. de Paris* 1: 654. 1938.
286. Dick, G. F., and W. C. Dine: Pituitary extract in Simmonds' disease. *Endocrinology* 22: 703. 1938.
287. Sheehan, H. L., and R. Murdoch: Post-partum necrosis of the anterior pituitary; pathological and clinical aspects. *J. Obst. & Gynaec. Brit. Emp.* 45: 456. 1938.
288. Straube, G.: Zur therapie der Simmondsschen Krankheit. *Klin. Wchnschr.* 17: 1016. 1938.
289. Sheehan, H. L., and R. Murdoch: Post-partum necrosis of the anterior pituitary: Effect of subsequent pregnancy. *Lancet* 2: 132. 1938.
290. Sheehan H. L., and R. Murdoch: Postpartum necrosis of the anterior pituitary. *Lancet* 1: 818. 1939.
291. Rea, C., and P. A. Hoover: Simmonds' disease; with case report. *Pennsylvania M. J.* 42: 27. 1938.
292. Goldzieher, M.: The endocrine glands. Appleton-Century Co. New York, 1939.
293. Thompson, W. O.: The hypothyroid states. *M. Clin. North America* 23: 175. 1939.
294. Solomon, H. A., A. Weiss and E. Hochstein: A clinical classification of hypothyroidism. *Endocrinology* 26: 785. 1940.
295. Rush, H.: Personal communication.
296. Turner, H. H.: Personal communication.
297. Atkinson, D.: Personal communication.
298. Canelo, C. K.: Personal communication.
299. Boyce, R., and C. F. Beadles: A further contribution to the study of the pathology of the hypophysis cerebri. *J. Path. & Bact.* 1: 359. 1893.
300. Veil, W. H.: Ueber das Verhalten der genitalen Funktionen beim Myxödem des Weibes. *Arch. f. Gynäk.* 107: 199. 1917.
301. Fahr, T.: Beiträge zur Pathologie der Hypophyse. *Deutsche med. Wchnschr.* 44: 206. 1918.
302. Reiche, F.: Zur klinischen Diagnose des Hypophysisschwundes. *Med. Klin.* 14: 984. 1918.
303. Reye, E.: Hypophysärer Kachexie. *München med. Wchnschr.* 66: 453. 1919.
304. Reye, E.: Hypophysärer Kachexie. *Deutsche med. Wchnschr.* 45: 703. 1919.
305. Reye, E.: Hypophysärer Kachexie. *Berl. Klin. Wchnschr.* 56: 790. 1919.
306. Simmonds M.: Juveniler Zwergwuchs bei Atrophie des Hypophysisvorderlappens. *München med. Wchnschr.* 66: 452. 1919.
307. Simmonds, M.: Zwergwuchs bei Atrophie des Hypophysisvorderlappens. *Deutsche med. Wchnschr.* 45: 487. 1919.
308. Feit, H.: Über hypophysäre Kachexie. *Med. Klin.* 16: 421. 1920.
309. Rouvillois, H., L. Reverchon and G. Worms: Lésions traumatiques de l'hypophyse dans les fractures de la base du crâne. *Bull. et mém. Soc. d. chirurgiens de Paris* 47: 685. 1921.
310. Reverchon, L., G. Worms and A. Rouquier: Lésions Traumatiques de l'hypophyse et paralysies multiples des nerfs craniens. *Presse méd.* 29: 741. 1921.
311. Lisser, H.: Hypopituitarism and its treatment. *Endocrinology* 6: 15. 1922.
312. Bauer, J.: Zwerge, hypophysäre Kachexie, Akromegalie. *Verhandl. deutsch. Kong. f. innere Med.* 35: 119. 1923.
313. Kiyono, H.: Über des Vorkommen von Plattenepithelherden in der Hypophyse. *Virchows Arch. f. path. Anat.* 252: 118. 1924.
314. Baló, J.: Über Nekrosen des Hypophysenvorderlappens und ihre Folgen. *Beitr. z. path. Anat. u. z. allg. Path.* 72: 599. 1924.
315. Urechia, C. I., and N. Elekes: La cachexie dite hypophysaire (maladie de Simmonds), *L'Encéphale* 21: 352. 1926 (abs. *J.A.M.A.* 87: 282. 1926).
316. Suchier, W.: Klinisches zur Simmondsschen Krankheit. *München med. Wchnschr.* 74: 1795. 1927.
317. Knauer, G. A.: Ueber zwei abortive Fälle von Hypophysenerkrankungen. *Centralbl. f. allg. Path. u. path. Anat.* 42: 1. 1928.
318. Karrenberg, C. L.: Morbus Simmonds (hypophysäre Kachexie) mit Hauterscheinungen. *Dermat. Wchnschr.* 87: 1876. 1928.
319. Karrenberg, C. L.: Fall von hypophysärer Kachexie (Morbus Simmonds mit universeller Neurodermitis). *Zentralbl. f Haut. u. Geschlechtskr.* 32: 557. 1930.
320. Riese, H.: Hypophysäre Kachexie. *Med. Welt.* 3: 1546. 1929.
321. Werthemann, Pathologisch-anatomische demonstrationen. *Klin. Wchnschr.* 9: 182. 1930.
322. Frazier, C. H.: A series of pituitary pictures. *Arch. Neurol. & Psychiat.* 23: 656. 1930.
323. Schellong, F.: Erkrankung des Hypophysenvorderlappens mit eigenartiger Blutdrucksenkung. *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* 42: 62. 1930.
324. Schellong, F.: Störung der Kreislaufregulation, ein neues symptom bei Insuffizienz des Hypophysenvorderlappens. *Klin. Wchnschr.* 10: 100. 1931.
325. Herman, K.: Zur Klinik und Diagnose der Simmondsschen Krankheit. *München med. Wchnschr.* 77: 1620. 1930.
326. Brunton, C. E.: A case of low metabolism with tumour of the pituitary region. *J. Physiol.* 71: 27. 1931.
327. McGovern, B. E.: Somnolence associated with pituitary cachexia. *Endocrinology* 16: 402. 1932.
328. Prüsener, L.: Hypophysäre Wachstumshemmung mit Kachexie beim Kinde. *Ztschr. f. Konstitutionsl hre* 17: 215. 1933.
329. Adler, L. D.: Hypophyseal cachexia. *South African M. J.* 7: 216. 1933.
330. Osman Hill, W. C.: Lorain's infantilism due to arrested development of the pituitary gland. *Ceylon J. Sc. Sect. D., Med. Sc.* 3: 115. 1933.
331. Kylin, E.: Ytterligare några fall med Simmonds leknande symtombilde. *Svenska läk.-tidning* 30: 905. 1933.
332. Barr, D. P.: Medical clinics. Pituitary cachexia (and Addison's disease). *J. Iowa State M. Soc.* 23: 599. 1933.
333. Striker, C.: A case of Simmonds' disease (Cachexia hypophyseopriva) with recovery. *J.A.M.A.* 101: 1994. 1933.
334. Kalk, H.: Zur Frage der Beziehung zwischen Hypophysenvorderlappen und Nebennierenrinde. *Deutsche med. Wchnschr.* 60: 893. 1934.
335. Abel, E., and P. Kissel: A propos d'un cas de cachexie hypophysaire. *Rev. franç. d'endocrinol.* 12: 287. 1934.
336. Aitken, R. S., and D. S. Russell: A case of Simmonds' syndrome. *Lancet* 2: 802. 1934.
337. Habán, G.: Kleinwuchs mit beginnender hypophysärer Kachexie bei Hypophysengangsgeschwulst. *Endokrinologie* 15: 158. 1935.
338. Müller, P.: Neuro-endokrines System und Blutbildung. *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* 47: 449. 1935.
339. Rau, L.: Pituitary cachexia (Simmonds' disease) treated with anterior lobe extract. *Lancet* 1: 1502. 1935.
340. May, E., and P. Robert: La cachexie hypophysaire ou syndrome de Simmonds. *Ann. de méd.* 38: 317. 1935.
341. Guggisberg, H.: Hypophysenstörungen als Folge des Fortpflanzungsvorganges. *Schweiz. med. Wchnschr.* 17: 34. 1936.

342. McGovern, B. E., and L. A. Frankel: Influenzal bronchopneumonia; bilateral alternating pneumothorax. *California & West. Med.* 49: 61. 1938.
343. Wilson, J.: Simmonds' disease. *Lancet.* 1: 951 1936.
344. Hellenthal, E.: Zur Therapie der Simmonds'schen Kachexie. *München med. Wchnschr.* 83: 1312. 1936.
345. Barr, D. P., and K. Mansbacher: The treatment of pituitary insufficiency and pituitary hyperfunction. *M. Clin. North America* 20: 379. 1936.
346. Merklen, P., M. Aron, L. Israel and A. Jacob: Tests histologiques de l'hypofonctionnement préhypophysaire dans certains cas de maigreur. *Bull. et mém. Soc. méd. d. hôp. de Paris* 52: 1360. 1936.
347. Merklen, P., M. Aron, L. Israel and A. Jacob: Du rôle de la préhypophyse dans certaines obésités et maigreurs. *Progrès méd.* 48: 1849. 1936.
348. Shelton, E. K., L. A. Cavanaugh and P. R. Patek: Fugitive acromegaly followed by pituitary cachexia. *Endocrinology* 20: 846. 1936.
349. Baltzan, D. M.: Pituitary cachexia. *Canad. M. A. J.* 36: 64. 1937.
350. Schur, M., and C. V. Medvei: Über Hypophysenvorderlappeninsuffizienz. *Wien. Arch. f. inn. Med.* 31: 67. 1937.
351. Snapper, I.: Het Verband Tusschen de Hypophyse eenerzijds, Functie van Maag en Beenmerg Anderzijds. *Nederl. tidschr. v. geneesk.* 81: 265. 1937.
352. Snapper, I., J. Groen, D. Hunter and L. J. Witts: Achlorhydria, anaemia and subacute combined degeneration in pituitary and gonadal insufficiency. *Quart. J. Med.* 30: 195. 1937.
353. Mainzer, F.: Ueber "kleine Endokrinologie." *Schweiz. med. Wchnschr.* 18: 513. 1937.
354. Merklen, P., and A. Jacob: In Discussion of article by Rohmer and Jung. *Bull. Soc. de pédiat. de Paris* 36: 528. 1938.
355. Thomson, A. P.: Sudden appearance of senility after an accident. *Lancet* 2: 135. 1938.
356. Pierini, E. A.: Caquexia hipofisaria ó sindrome de Simmonds. *Rev. sud-am. de endocrinol.* 21: 630. 1938.
357. Lockhart, J. C.: from Peter Bent Brigham Hospital, Boston, Mass. Personal Communication.
358. Feiling, A.: Simmonds' disease (Pituitary cachexia). *Proc. Roy. Soc. Med.* 32: 209. 1939.
359. Spence, A. W., and L. J. Witts: Substitution therapy in hypopituitarism. *Quart. J. Med.* 8: 69. 1939.
360. Cahane, M., and T. Cahane: Insuffisance pituitaire et schizophrénie. *Ann. méd. psychol.* 97: 214. 1939.
361. Kerppola, W.: Über Symptome von Hypophysenschwäche in Fällen von Untergewicht. *Acta med. Scandinav.* 99: 287. 1939 (abs. *J.A.M.A.* 113: 188. 1939).
362. Duvoir, M., L. Pollet, F. Layani and J. Chenebault: Syndrome de Simmonds et diabète insipide. Remarques pathogeniques et therapeutiques. *Bull. et mém. Soc. méd. d. hôp. de Paris* 55: 483. 1939.
363. Loos, D.: Beitrag zur Frage des Simmondsschen Syndroms. *Deutsche med. Wchnschr.* 65: 1115. 1939.
364. Kylin, E., and E. Dicker: Le rôle de l'hypophyse dans la pathogénie de l'alopécie totale. *Acta med. Scandinav.* 100: 485. 1939 (abs. *J.A.M.A.* 113: 1526. 1939).
365. Canavan, M.: Simmonds' disease (Pituitary cachexia) in an aged man with dementia praecox. *Arch. Path.* 29: 310. 1940.
366. Nonne, M.: Hypophysenerkrankungen. *Deutsche med. Wchnschr.* 42: 1369. 1916.
367. Worms, G., and G. Delater: Destruction totale de l'hypophyse par tumeur d'origine rhinopharyngée sans syndrome dit hypophysaire. *Rev. Neurol.* 32: 361. 1925.
368. Kurokawa, K.: A case of Simmonds' disease. abs. *Am. J. Dis. Child.* 33: 834. 1927 (orig. *J. Ped. Tokyo* p. 1815, Dec. 20, 1926).
369. Ibotson, E. C. B.: A case resembling Addison's disease. *Lancet* 1: 79. 1928.
370. Reye, L.: Die ersten klinischen Symptome bei Schwund des Hypophysenvorderlappens (Simmondssche Krankheit), und ihre erfolgreiche Behandlung. *Deutsche med. Wchnschr.* 54: 696. 1928.
371. Boenheim, F.: Zur Kenntnis der Laurence-Biedlschen Krankheit. *Endokrinologie* 4: 263. 1929.
372. Goebel, F.: "Hypophysäre Kachexie" beim Kleinkind ohne Zwergwuchs bei intakter Hypophyse. *Ztschr. f. Kinderh.* 53: 575. 1932.
373. Signorelli, S.: Diabete, nanismo e cachessia ipofisaria con reperto di ependimopartia granulare nel pavimento del III° ventricolo. *Policlinico* (Sez .Prat.) 41: 1228. 1934.
374. Vanucci, F.: Sindrome di Simmonds e terapia preipofisaria. abs. *Kong. Zentralbl. f. d. ges. inn. Med.* 81: 329. 1935 (orig. *Giorn. Clin. med.* 16: 203. 1935).
375. Gravano, L., and A. Casanegra: Caquexia hipofisiaria de Simmonds. *Senama méd.* 42: 649. 1935.
376. Landabure, P.: Estado caquéctico y diabetes (¿Enfermedad de Simmonds?). *Semana méd.* 42: 654. 1935.
377. Khavine, J. B.: Influence de la grossesse et de l'accouchement sur les glandes a sécrétion interne. *Rev. franç d'endocrinol.* 14: 307. 1936.
378. Samet-Mandels, S., and K. Sciesinski: Tumeur du cervelet (ependymogliome) avec syndrome secondaire de Simmonds chez une fillette de 8 ans. Influence de la médication par les extraits de lobe antérieur d'hypophyse. *Rev. franç de pediat.* 13: 525. 1937.
379. Geldrich, J.: Die Simmondssche Krankheit im Kindesalter. *Monatschr. f. Kinderh.* 80: 103. 1939.
380. Westphal, C.: Ueber zwei Fälle von Syphilis des Gehirns. *Allg. Ztschr. f. Psychiat.* 20: 481. 1863.
381. Kufs: Beitrag zur Syphilis des Gehirns und der Hypophysis und zur Differentialdiagnose zwischen der Tuberculose und Syphilis des Centralnervensystems. *Arch. f. Psychiat.* 39: 134. 1904.
382. Froboese, C.: Die tuberkulöse Erkrankung der Hypophysis, insbesondere über die primäre Form. *Zentralbl. f. allg. Path. u. path. Anat.* 29: 145. 1918.
383. Krumbhaar, E. B.: Pituitary disorders in their relation to acromegaly (hyper-prepituitarism) with suggestions for the use of a more precise terminology. *M. Clin. North America* 5: 927. 1921.
384. Mieremet, C. W. G.: Hypophysäre Kachexia, Coma pituitarium und Lethargia pituitaria. abs. *Kong. Zentralbl. f. d. ges. inn. Med.* 27: 156. 1923 (orig. *Geneesk. bl. u. klin. en lab. v. d. prakt.* 23: 235. 1922).
385. Müller, E.: Über einen Fall von fast völligem Schwund der Schilddrüse und Hypophyse. *Klin. Wchnschr.* 2: 1576. 1923.
386. Sheehan, H. L.: Post-partum necrosis of the anterior pituitary, *J. Path. & Bact.* 45: 189. 1937.
387. Kraus, E. J.: Wie lässt sich die Annahme eines Corticotropen Hyperpituitarismus beim Menschen Morphologisch Stützen. *Klin. Wchnschr.* 16: 1528. 1937.
388. Formanek, F.: Zur Kasuistik der Hypophysengangsgeschwülste. *Wien. klin. Wchnschr.* 22: 603. 1909.
389. Hönlinger, H., and W. Stricker: Ein Plattenepithelzystopapillon des Processus lingualis des Hypophysenvorderlappens bei einem Falle von hypophysärer Kachexie. *Frankfurt Ztschr. f. Path.* 29: 492. 1923.
390. Lang, F. J.: Ein Plattenepithelzystopapillon (Erdheimscher Hypophysengangtumor) des Infundibularbereiches mit hypophysärer Kachexie. *Wien. klin. Wchnschr.* 37: 977. 1924.
391. Baudouin, A., J. Lhermitte and J. Lereboullet: Un cas de pinéalome: absence de macrogenitosome précoce. Le problème de la cachexie hypophysaire. *Rev. neurol.* 1: 388. 1932.
392. De Gennes, L., J. Delarue and Rogé: Maladie de Simmonds. Étude anatomo-clinique. *Bull. et mém. Soc. méd. d. hôp. de Paris* 52: 387. 1936.
393. Lhermitte, J., DeMartel, P. Guillaume and J. Ajuriaguerra: Syndrome de cachexie progressive. Spongioblastome infiltré du 3e ventricule. Le problème de la maladie de Simmonds. *Rev. neurol.* 71: 166. 1939.
394. Wagner, E.: Tuberkel der Glandula pituitaria. *Arch. d. Heilk.* 3: 381. 1862.
395. Cyran, E.: Hypophysenschädigung durch Schädelbasisfraktur. *Deutsche med. Wchnschr.* 44: 1261. 1918.
396. Schaefer, H.: Beitrag zur Lehre von den Entzündungen spezifischer und nichtspezifischer Natur in der Hypophyse. *Zentralbl. f. allg. Path. u. path. Anat.* 30: 520. 1920.
397. Marañon, G.: Diabetes insipidus as a hypopituitary syndrome. *Endocrinology* 5: 159. 1921.

398. Reinhardt, A.: Zur Pathologie der Hypophyse. *Klin. Wchnschr.* 1: 2309. 1922.
399. Gerlóczy, G.: Aussprache l. *klin. Wchnschr.* 2:902. 1923.
400. Baló, J.: Über die Nekrose des Vorderlappens der Hypophyse und deren Folgen. *Klin. Wchnschr.* 2: 902. 1923.
401. Szondy: Aussprache. *Klin. Wchnschr.* 2: 902. 1923.
402. Simonds, J. P., and W. W. Brandes: Pathology of the hypophysis. III. Chronic hypophysitis; fibrosis. *J.A.M.A.* 84: 1408. 1925.
403. Illig. W.: Geschwülste der Hypophyse bzw. der Hypophysengegend und Zwischenhirn. *Virchows Arch. f. path. Anat.* 270: 549. 1928.
404. Boenheim, F.: Zur Kenntnis der hypophysären Kachexie. *Verhandl. d deutsch. Gesellsch. f. inn. Med.* 42: 644. 1930.
405. Boenheim, F., and F. Heimann: Beitrag zur Klinik der hypophysären Kachexie. *Deutsche med. Wchnshcr.* 56: 1818. 1930.
406. Schellong, F.: Weiteres über das Symptom der Blutdrucksenkung nach Körperarbeit. *Klin. Wchnschr.* 11: 53. 1932.
407. Oppenheimer, B. S.: In Discussion of article by Farquharson and Graham. *Tr. A. Am. Physicians* 46: 160. 1931.
408. Schlayer, C. R.: Magerkeit und Magersucht. *Deutsche med. Wchnschr.* 60: 158. 1934.
409. Berman, L.: The treatment of a type of malnutrition (Simmonds' disease like) with prepituitary growth hormone. *New York State J. Med.* 35: 916. 1935.
410. Curschmann, H.: Die Simmondssche Krankheit. Aussprache, *Med. Klin.* 32: 895. 1936.
411. Berblinger, W.: Hypophysentuberkulose als Todesursache. *Schweiz. med. Wchnschr.* 69: 1217. 1939.
412. Farquharson, R. F., and H. H. Hyland: Anorexia nervosa. *J.A.M.A.* 111: 1085. 1938.
413. Bruckner, W. J., C. H. Wies and P. H. Lavietes: Anorexia nervosa and pituitary cachexia. *Am. J. M. Sc.* 196: 663. 1938.
414. Meyer, H.: Über Magersucht. *Deutsche med. Wchnschr.* 64: 1400. 1938.
415. Nicolle, G.: Pre-psychotic anorexia. *Proc. Roy. Soc. Med.* 32: 153. 1939.
416. Sheehan, H. L.: Post-partum necrosis of the anterior pituitary. *Edinburgh M. J.* 45: 13. 1938.
417. Effkemann, G., and F. Müller-Jager: Über das Auftreten von Hypophysenvorderlappen-Insuffizienzen nach starken Post-partum-Blutungen. *Arch. f. Gynäk.* 168: 867. 1939.
418. Brown, C. E., and L. F. Eder: Acute puerperal hypophyseal necrosis. *Am. J. M. Sc.* 198: 166. 1939.
419. Gotshalk, H., and I. Tilden: Necrosis of the anterior pituitary following parturition. *J.A.M.A.* 114: 33. 1940.
420. Kotte, J. H., and A. R. Vonderahe: The Houssay phenomenon in man. *J.A.M.A.* 114: 950. 1940.
421. Mussio-Fournier, M. J. C.: Syndrome hydropigène et insuffisance thyroidienne. *Bull. Acad. de méd., Paris* 93: 691. 1925.
422. Hertzler, A. E.: Myxedema with ascites: report of a case. *Am. J. M. Sc.* 191: 245. 1906.
423. Evans, W.: Myxedema with ascites and bladder atony. *Endocrinology* 16: 409. 1932.
424. Escamilla, R. F., H. Lisser and H. C. Shepardson: Internal myxedema: report of a case showing ascites, cardiac, intestinal and bladder atony, menorrhagia, secondary anemia, and associated carotinemia, *Ann. Int. Med.* 9: 297. 1935.
425. Hanssen, P.: Myxoedema and ascites. *Acta Med. Scandinav.* Suppl. 90: 277. 1938.
426. Claude, H., and M. Sourdel: Hémosidérose viscérale et insuffisance pluriglandulaire. *Bull. et mém. Soc. méd. d. hôp. de Paris* 34: 32. 1912.
427. Althausen, T. L., and W. J. Kerr: Hemochromatosis. A report of three cases with results of insulin therapy in one case. *Endocrinology* 11: 377. 1927.
428. Althausen, T. L., and W. J. Kerr: Hemochromatosis II. A report of three cases with endocrine disturbances and notes on a previously reported case. Discussion of etiology. *Endocrinology* 17: 621. 1933.
429. Bauer, J.: Endocrine aspects of sprue: their relation to the pituitary syndrome in anorexia nervosa. *J. Trop. Med.* 42: 245. 1939.
430. Mollaret, P., and N. Peron: Anorexie mentale à forme grave. Nécessité vitale de la cure d'alimentation. *Bull. et mém Soc. méd. d. hôp. de Paris* 2: 1716. 1938.
431. Berkman, J. M.: Anorexia nervosa, anorexia, inanition, and low basal metabolic rate. *Am. J. M. Sc.* 180: 411. 1930.
432. Houssay, B. A., and A. Biasotti: Le diabète pancreatique des Chiens hypophysectomisés. *Compt. rend. Soc. de biol.* 105: 121. 1930.
433. Rolleston, H. D.: The endocrine organs in health and disease. Oxford University Press, London, 1936.
434. Wilder, J.: Ein neues hypophysäres Krankheitsbild: Die hypophysäre Spontanhypoglykämie. *Deutsche Ztschr. f. Nervenh.* 112: 192. 1930.
435. Corkill, A. B., H. P. Marks and W. E. White: Relation of the pituitary gland to the action of insulin and adrenalin. *J. Physiol.* 80: 193. 1933.
436. Mahoney, W.: Hypoglycemia following hypophysectomy as explanation of so-called cachexia hypophyseopriva. *Ann. Surg.* 99: 387. 1934.
437. Crowe, S. J., H. Cushing and J. Homans: Experimental hypophysectomy. *Bull. Johns Hopkins Hosp.* 21: 127. 1910.
438. Smith, P. E.: The disabilities caused by hypophysectomy and their repair. *J.A.M.A.* 88: 158. 1927.
439. Evans, H. M., K. Meyer, R. Pencharz and M. E. Simpson: Cure of the cachexia following hypophysectomy by administration of the growth hormone and its relation to the resulting adrenocortical repair. *Science* 75: 442. 1932.
440. Houssay, B. A.: The influence of the pituitary on basal metabolism and on specific dynamic action. *Endocrinology* 18: 409. 1934.
441. Roussy, G., and M. Mosinger: Hypothalamus et hypophyse: Le tuber cinereum et son rôle dans les principales fonctions du métabolisme: Métabolisme de l'eau des glucides et des lipides. *Ann. de méd.* 33: 193. 1933.
442. Bailey, P., and F. Bremer: Recherches experimentales sur le diabète insipide et le syndrome adiposogénital. *Compt. rend. Soc. de biol.* 86: 925. 1922.
443. Cushing, H.: Posterior pituitary activity from the anatomical standpoint. *Am. J. Path.* 9: 539. 1933.
444. Fisher, C., W. R. Ingram and S. W. Ranson: Diabetes insipidus and the neuro-hormonal control of water balance: A contribution to the structure and function of the hypothalamico-hypophyseal system. Edwards Bros., Ann Arbor. 1938.
445. Solis-Cohen, S., and E. Weiss: Dystrophia adiposogenitalis with atypical retinitis pigmentosa and mental defficiency—the Laurence-Biedl syndrome. *Am. J. M. Sc.* 169: 489. 1925.
446. Sheldon, J. H.: Anorexia nervosa. *Lancet* 1: 369. 1937.
447. Melchionna, R. H., and R. A. Moore: The pharyngeal pituitary gland. *Am. J. Path.* 14: 763. 1938.
448. Heidkamp, H.: Beitrag zur Tuberkulose der Hypophyse. *Virchows Arch. f. path. anat.* 210: 445. 1912.
449. Kollarits, J.: Hypophysistumoren ohne Akromegalie. *Deutsche Ztschr. f. Nervenh.* 23: 88. 1904.
450. Müller-Deham, A.: Fettsucht und Magersucht im Alter. *Wien. klin. Wchnschr.* 48: 950. 1935.
451. Rougean, R., and M. Rougean: Anorexie mentale et hypophyse. *Ann. méd.-psychol.* 95: 634. 1937.
452. Cervera, L., A. Folch and B. Benaiges: Cachexie hypophysaire et anorexie mentale. *Rev. franç. d'endocrinol.* 15: 291. 1937.
453. Peron, N.: Défense de l'anorexie mentale, *Paris méd.* 109: 65. 1938.
454. Comby, J.: Maladie de Simmonds et anorexie mentale. *Arch. de méd. d. enf.* 41: 638. 1938.
455. Morlock, C. G.: Anorexia nervosa. *Proc. Staff Meet., Mayo Clin.* 14: 24. 1939.
456. Pagniez, P.: Anorexie mentale et hypophyse, *Presse méd.* 47: 668. 1939.
457. Berkman, J. M.: Functional anorexia and functional vomiting: their relation to anorexia nervosa. *M. Clin. North America* 23: 901. 1939.
458. Vieux, N., and R. Fau: Les éléments cliniques du diagnostic et du prognostic de l'anorexie mentale. *Paris méd.* 29: 177. 1939.
459. Chatagnon, P., and P. Scherrer: L'Anorexie mentale et son traitment d'urgence, *Presse méd.* 47: 1277. 1939 (abs. *J.A.M.A.* 113: 1682. 1939).

460. Myers, J. W.: Mental anorexia simulating pituitary cachexia. *Southwestern Med.* 23: 367. 1939.
461. Davis, H. P.: Anorexia nervosa. *Endocrinology* 25: 991. 1939.
462. Ryle, J. A.: Anorexia nervosa. *Lancet* 2: 893. 1936.

APPENDIX

(Other articles on the clinical aspects of Simmonds' disease consulted but not referred to in the text).

Froment, J.: Les syndromes hypophysaires: Clinique et thérapeutic. *Rev. neurol.* 38: 649. 1922.
Mouzon, J.: Les syndromes hypophysaires. *Paris méd.* 45: 47. 1922.
Cushing, H.: The pituitary gland as now known. *Lancet* 2: 899. 1925.
Boenheim, F.: Hypophysäre Krankheiten. *Ztschr. f. ärtzl. Fortbild.* 26: 617. 1929.
Reye, and Schürmann; Über Simmondssche Krankheit. *Klin. Wchnschr.* 9: 525. 1930.
Lichtwitz, L.: Hypophysäre Symptome und Hypophysenkrankheiten. *Verhandl. d. deutsch. Gesselsch. f. inn. Med.* 42: 1930.
DeJean, C.: Les syndromes hypophysaires. *Gaz. d. hôp.* 105: 337. 1932.
Grafe, E.: Zur Einteilung der Hypophysenvorderlappenerkrankungen, *Deutsche med. Wchnschr.* 58: 576. 1932.
Steinitz, E.: Über hypophysäre Kachexie und verwandte Zustände. *Deutsche med. Wchnschr.* 58: 1323. 1932.
Grafe, E.: Endogene Magerkeit. *Zentralbl. f. inn. Med.* 54: 365. 1933.
Berblinger, W.: Die Hypophysenkrankheiten. *Med. Klin.* 29: 831. 1933.
Schulmann, E., and H. Mamou: Diagnostic des cachexies endocriniennes. *Progrès. méd.* 1179. 1933.
Kylin, E.: Ytterligare några fall med Simmondslikande symptombilde. *Svenska läk.-tidning* 30: 934. 1933.
Bauer, J.: Neuere Anschauungen über Funktions-störungen der Hypophyse. *Klin. Wchnschr.* 12: 1553. 1933.
Kylin, E.: Om Kolhydratomsättningen vid essentiell hypertoni, akromegali och Simmonds sjukdom. *Svenska läk.-tidning* 30: 1216. 1933.
Popper, L.: Subakute Lymphogranulomatose unter dem Bilde der Simmondschen Kachexie. *Med. Klin.* 29: 1644. 1933.
Mislowitzer, E., and L. Stanoyévitch: Contribution a la pathologie fonctionnelle et au diagnostic de la cachexie hypophysaire (Maladie de Simmonds). *Compt. rend. soc. de biol.* 115: 881. 1933.
Kylin, E.: Über Kohlehydratumsatz bei essentieller Hypertonie, Akromegalie und Simmondsscher Krankheit. *Med. Klin.* 30: 153. 1934.
Kylin, E.: On the contrast in the clinical features of Simmonds' disease and essential hypertension. *Acta med. Scandinav.* 84: Suppl. 59: 222. 1934.
Nurnberger, L.: Spätstörungen nach Schwangerschaft, Geburt und Wochenbett. *Deutsche med. Wchnschr.* 60: 1415. 1934.
Kehrer, E.: Endokrine Syndrome in der Gravidität und nach dem Puerperium. *Ztschr. f. Geburtsch. u. Gynäk.* 110: 105. 1935.
Fiessinger, N.: Les syndromes hypophysaires. *J. d. practiciens* 50: 97. 1936.
Stroebe, F.: Die Simmondssche Krankheit. Einleitung. *Med. Klin.* 32: 859. 1936.
Reye, E.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 860. 1936.
Berblinger, W.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 861. 1936.
Kylin, E., and H. Elmquist: Über den Blutnatriumspiegel bei essentieller Hypertonie und Simmondsscher Krankheit, *Acta med. Scandinav.* 88: 507. 1936.
Bickel, G.: L'Insuffisance antéhypophysaire. Presse méd. 44: 1204. 1936.
Raab, W.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 897. 1936.
Schürmann, P.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 1387. 1936.
Schellong, F.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 1388. 1936.
Grafe, E.: Die Simmondssche Krankheit. Aussprache. *Med. Klin.* 32: 1389. 1936.
Raab, W.: Klinik der Hypophysen-Erkrankungen. *Wien. klin. Wchnschr.* 50: 537. 1937.
Falta, W.: Bemerkungen zur Pathologie der hypophysären Erkrankungen. *Wien. med. Wchnschr.* 87: 457. 1937; abs. *J.A.M.A.* 108: 2172. 1937.
Paingault, M.: Maladie de Simmonds. Thèse de Paris, 1937.
Campbell, E. H.: Clinical aspects of changes in the anterior lobe of the pituitary gland. *Albany M. Ann.* 56: 85. 1937.
Loeper, M., and J. B. Sainton: Le diagnostic de la cachexie hypophysaire. *Progrès méd.* 1409. 1937.
Raab, W.: Klinik der Hypophysenerkrankungen. *Wien. med. Wchnschr.* 87: 1103. 1937.
Di Guglielmo, G.: Patologia e terapia delle sindromi neuro-ipofisarie. *Riforma med.* 53: 1782. 1937.
Jores, A.: Über die Funktionen der Hypophyse. *Klin. Wchnschr* 17: 689. 1938.
Pardee, I. H.: in Discussion of Chapter XXXV, pp. 614–615, of Herrick, "The Pituitary Gland," Williams and Wilkins, Baltimore, 1938. Publ. by Assoc. for Research in Nerv. and Mental Dis.
Ravoire, J.: Maladie de Simmonds, *Gaz. d. hôp.* 112: 125. 1939.
Alvarez, W. C.: Simmonds' disease and anorexia nervosa, *Am. J. Digest. Dis. & Nutrition* 6: 276. 1939.

The Quantitative Variations of the Pancreatic Islet Tissue in a Mixed Series of Cases

[Pancreatic Pathology]

WILLIAM SUSMAN, M.D.

From the Department of Pathology, The University of Manchester, Manchester, England

A HISTOLOGICAL SURVEY of the pancreas in a large series of unselected cases quickly discloses the fact that the amount of islet tissue varies a great deal from case to case. Heilberg (1), and later, Ogilvie (2), devised methods for estimating the weight of an average islet and also the number of islets in a given pancreas. From these data it was possible, too, to calculate by weight, the proportion of islet tissue in the pancreas. These figures were arrived at through area readings.

Ogilvie's work has been confined to the creation of normal standards, and to the age variations. In the present series, however, the chief consideration is the possible effects of disease on the amount of islet tissue present.

METHODS

The amount of islet tissue in each section was estimated by area readings made with a planimeter. In a number of cases readings were made on sections from several parts of the same pancreas; these readings corresponded so closely as to confirm the view that islet tissue is distributed fairly uniformly, and that readings from any one section were representative.

All of the islets in 10 standard fields of each section, chosen at random, were drawn under the low power (⅔″) by the camera lucida. The islet areas in each field were then calculated with a planimeter. The whole field including both islet and acinar tissue measured 110 planimeter units. One planimeter unit was equivalent to 11.8 square centimeters of the camera lucida drawings, and these drawings had been magnified to 77.8 times the original size in the sections. At first the results were classified on the basis of planimeter units but this was altered eventually to the percentage of islet tissue to pancreatic tissue as a whole; for this reason the percentage unit for the various groups may appear unusual. The following table gives the corresponding planimeter unit (P.U.) and percentage values.

1 P.U.=0.9 per cent; 2 P.U.=1.8 per cent; 3 P.U.=2.7 per cent; 4 P.U.=3.6 per cent; 5 P.U.=4.6 per cent and 6 P.U.=5.5 per cent.

MATERIAL

The present series consists of 202 unselected cases in which sections of the pancreas were available. Of these 202 cases, 5 were without complete details, leaving 197 cases with all the necessary data. The full series contained 51 diabetics but 4 had incomplete information available leaving 47 cases in all, for parts of this investigation. Nondiabetics with full data numbered 150. The sections had been prepared by the paraffin method and stained by haemalum and eosin. The age and sex distribution is shown in table 1.

TABLE 1. AGE AND SEX DISTRIBUTION OF DIABETICS AND THE WHOLE SERIES

Age Group, years	Male		Female		Totals	
	Diabetic group	Whole series	Diabetic group	Whole series	Diabetic group	Whole series
0– 9	1	23	0	8	1	31
10–19	0	5	0	5	0	10
20–29	3	7	9	20	12	27
30–39	0	3	7	15	7	18
40–49	3	19	3	16	6	35
50–59	4	25	4	14	8	39
60–69	6	18	4	13	10	31
70+	1	4	2	3	3	6
No details				1	4	5
Totals	18	103	29	94	51	202

RESULTS

After inspecting the results it became obvious that there was a number of cases with very low readings, and it seemed that these might constitute a definite group, possibly associated with diabetes mellitus.

Received for publication September 26, 1941.

Cases with Low Islet Tissue Content

Diabetic group. Although the normal range of islet area readings is discussed later in detail, a summary of those findings is essential at this stage in order to provide a normal standard. In adults the majority of the islet readings were between 0.9 and 2.7 per cent, while in infants the range was between 0.9 and 3.6 per cent of islet tissue per field of pancreas. For the purposes of this investigation it is assumed that these constitute the normal limits in adults and in infants respectively. With these basic standards available it is possible to appreciate the findings in the diabetic group.

TABLE 2. AGE AND SEX ANALYSIS OF DIABETIC CASES WITH READINGS UNDER 1.36 PER CENT

Age Group, years	Male		Female		Totals		
	0–0.9%	0.9–1.27%	0–0.9%	0.9–1.27%	0–0.9%	0.9–1.27%	Total
0– 9	1	0	0	0	1	0	1
10–19	0	0	0	0	0	0	0
20–29	1	1	7	2	8	3	11
30–39	0	0	5	1	5	1	6
40–49	1	2	1	1	2	3	5
50–59	1	2	2	1	3	3	6
60–69	3	1	2	1	5	2	7
70+	1	0	2	0	3	0	3
No details					2	2	4
Totals	8	6	19	6	29	14	43

There were 51 cases of diabetes mellitus in this series, of which the age and sex distribution is shown in table 1.

Of the 51 cases in the diabetic group

29 had islet area readings under 0.9 per cent; 14, with readings between 0.9 and 1.3 per cent; 2, with readings between 1.4 and 1.7 per cent; 4, with readings between 1.8 and 2.6 per cent; 1, with readings between 2.7 and 3.6 per cent and 1, with readings over 4.6 per cent.

Over one-half of the diabetic cases, 29 in all, have islet area readings under 0.9 per cent, while 43 of the total of 51 cases are under 1.3 per cent. The arithmetic average of the area readings in the 51 diabetic cases is 0.99 per cent with the readings ranging from 0.17 to 4.6 per cent; 22 cases had values over 0.9 per cent including 16 with readings between 0.9 and 1.8 per cent. As these 16 cases constitute the bulk of diabetics with higher readings, they can be considered separately. Six showed hyalin degeneration varying from scattered patches to extensive involvement of many islets; others had congestion, hemorrhage, atheroma, or partial fibrosis of the islets. Thus, these high readings are not necessarily due to healthy or functioning islet tissue. If allowance is made for this fact it becomes evident that the typical case of diabetes mellitus had an average islet tissue value of under 0.9 per cent.

Diabetic cases with readings over 1.8 per cent numbered 6 in all. Of these, 2 showed extensive islet degeneration, and 1 extensive islet hemorrhage. In the remaining 3 cases there was nothing extraneous to account for the high readings. One was a case that had not been active for 5 years (reading 2.1%); the possibility exists that here islet tissue repair had taken place in the form of hyperplasia. A similar explanation might account for the high readings in the remaining 2 cases.

Nondiabetic cases with readings under 0.9 per cent. The whole series included 4 nondiabetics with readings under 0.9 per cent. Details concerning these cases are available in table 3.

Thus, readings under 0.9 per cent are highly suggestive of diabetes mellitus. The whole series contained only 4 nondiabetics (2%) with these low readings, while Ogilvie's series had 4 per cent of cases of this type. In view of the absolute predominance of diabetics among these cases, the 'under 0.9 per cent' group can be considered with justification to constitute a section showing islet tissue deficiency.

Cases with a Normal Range of Islet Tissue Content

In order to establish what constitutes the normal islet tissue content, two methods are available; *a*) the readings in cases in which the disease of the patient had not had sufficient time to cause any appreciable islet changes could be considered to be within normal limits; *b*) it could be assumed that as the greater proportion of cases in an unselected series will have normal readings, an examination of the frequencies of the readings in the whole series might be of value. Adults and infants are studied separately.

TABLE 3. NONDIABETIC CASES WITH READINGS UNDER 0.9 PER CENT

Case	Sex, Age	Disease	Islet Area Values, %
48	F 23	Diabetes insipidus	0.86
172	M 53	Lobar pneumonia	0.77
217	M 51	Myocardial failure	0.68
386	M 58	Acute pericarditis, adrenal atrophy	0.72

Adults. An appreciable increase in the amount of islet tissue could occur only through hypertrophy or hyperplasia or both, and some time would necessarily elapse before these processes could be established. Hence an increased islet tissue content could be expected only in association with chronic diseases, while in cases of acute diseases the amount of islet tissue present is more likely to be within normal limits. There is the possibility, however, that some long-

standing process, not of a disabling character and of the type that might have been overlooked at a post-mortem examination, could have altered the islet tissue content in what appeared to be an acute case. This possibility must be kept in mind.

In the present series there were 23 cases of acute disease with no obvious chronic complications. Of these, 10 were males and 13 females. The readings obtained in this group were as follows.

1 with average reading under 0.9 per cent, 18 with average reading between 0.9 and 1.8 per cent, 3 with average reading between 1.8 and 2.7 per cent, and 1 with average reading between 2.7 and 3.6 per cent.

Accordingly, readings between 0.9 and 1.8 per cent probably represent the normal range in islet tissue content. This is further implied by the arithmetic average of 1.6 per cent for the 23 cases.

The problem can be approached from another direction. It is reasonable to suppose that in most of the nondiabetic cases in the whole series the amount of the islet tissue will not be seriously disturbed. If this be so, then an examination of the incidence of the islet tissue values might give some indication as to what consistutes the normal range.

Among the nondiabetic cases excluding infants there were

4 with readings under 0.9 per cent, 64 with readings between 0.9 and 1.8 per cent, 46 with readings between 1.8 and 2.7 per cent, 22 with readings between 2.7 and 3.6 per cent, 6 with readings between 3.6 and 4.6 per cent, 5 with readings between 4.6 and 5.5 per cent, and 5 with readings over 5.5 per cent.

The 0.9 to *1.8 per cent group* shows the highest frequency (35%) while the *1.8 to 2.7 per cent group* claims 25 per cent. Both groups combined account for 60 per cent of all of the adult cases. Hence, it can be assumed with safety that the normal range lies between 0.9 and 2.7 per cent while over 3.6 per cent might be considered high.

Infants. In all, there were 25 cases under 3 years of age; 21 were under one year and 4 were between 1 and 2 years. As all but 4 of the cases were under one year of age, observations on the infant group were limited to this section. Of the cases under one year of age there were

7 with readings between 0.9 and 1.8 per cent, 7 with readings between 1.8 and 2.7 per cent, 3 with readings between 2.7 and 3.6 per cent, 1 with readings between 3.6 and 4.6 per cent, 1 with readings between 4.6 and 5.5 per cent, and 2 with readings between 5.5 and 6.4 per cent.

Fourteen or two-thirds of these cases had readings up to 2.7 per cent, and 17 up to 3.6 per cent. The arithmetic mean for the values in these 21 cases was 2.5 per cent with readings from 1.1 to 5.6 per cent. Thus the indications are that the normal range in the infant group is between 0.9 and 2.7 per cent, and this probably should be extended to cover the 2.7 per cent group as well (up to 3.6%). Therefore, one may conclude that there appears to be a tendency for the higher readings to be more frequent among infants. That the normal for infants is higher than that for adults is indicated by the results obtained by Ogilvie. This is further supported by the clinical evidence of various workers that the blood sugar in infants is lower than in adults.

TABLE 4. DETAILS OF CASES WITH ISLET AREA READINGS OVER 3.6 PER CENT

No. of Cases	Islet Group	Case	Sex, Age	Disease	Islet Reading[1]
7	3.6 to 4.6%	28	M, 66	Pulm. tuberc.	4.4
		115	M, 3 mo.	Acute bronchiolitis	3.7
		173	M, 55	Pernicious anemia	3.8
		193	M, 45	Syphilitic aortitis	4.2
		205	F, 7	Chloroma	3.7
		332	F, 54	C.M.F., atrophy of thyroid	4.0
		361	M, 18	Addison's disease, ulc. enteritis	4.0
6	4.6 to 5.4%	31	M, 12	Tuberc. of spine, bronchopneumonia	5.2
		188	M, 6 mo.	Lymphosarcoma, cap. bronchitis	4.8
		211	F, 43	Otitis media, cerebral abscess, pyemia	4.9
		215	F, 58	Carc. esophagus	5.1
		270	M, 48	Cerebral hemorrhage, acute encephalitis	5.2
		376	M, 62	Diabetes mellitus, chronic Pb poison, pyemia	4.6
7	5.5% and over	51	M, 61	Chr. pulm. tuberc.	11.6
		91	M, 56	Pellagra, carc. of tongue	7.8
		329	M, 3 mo.	Cerebrospinal meningitis	5.5
		337	M, 41	Ulc. colitis	6.2
		342	F, 5 mo.	Bronchopneumonia	5.6
		349	M, 1	Bronchopneumonia	7.6
		359	M, 40	Chr. myeloid leuk.	6.2

[1] Percentage ratio of islet tissue to pancreas.

Cases with High Islet Tissue Content

After excluding all the cases with readings up to 3.6 per cent, those that remain can be considered definitely as of the high islet tissue content group. In all there were 20 such cases and their details are presented in tables 4 and 5.

Table 5 shows that there were no cases of this type between 20 and 40 years of age which suggests the existence of two distinct groups, one under 20 years and another over 40 years of age.

There were 8 cases under 20 years of age. Of these 5 were one year of age or under, and all were cases showing acute diseases unlikely to affect the islet tissue quantitatively; hence it can be assumed that the high readings were of congenital origin.

A disease analysis of the group of 20 cases showed that tuberculosis had claimed 3, pernicious anemia and other blood diseases 3, and malignant disease 3 cases each. These, together with the 5 cases of one year of age and under, account for 13 of the 20 cases (one case was included in two groups).

TABLE 5. AGE AND SEX INCIDENCE OF CASES WITH AVERAGE ISLET AREA PER FIELD VALUE OVER 3.6 PER CENT

Age Group, years	Male	Female	Total
0– 1	3	1	4
1– 9	1	1	2
10–19	2	0	2
20–29	0	0	0
30–39	0	0	0
40–49	4	1	5
50–59	2	2	4
60–69	3	0	3
70+	0	0	0
Totals	15	5	20

If the arithmetic means for the group of cases with acute diseases can be taken as the normal reading, then it becomes evident (table 6) that in blood diseases, malignant diseases, tuberculosis, syphilis, and even in chronic diseases as a whole, the average is about twice that for the normal. The disease conditions in these groups are for the most part diseases of the chronic and proliferative types. In the process of cell proliferation an increased demand for carbohydrate has been observed, and it may be that the apparent association of chronic diseases with an increased islet tissue content is brought about by an increased carbohydrate metabolism.

Islet Tissue Content in Relation to Size and Number of Islets

Variation in islet tissue content can only occur through alterations in the size or in the number of islets, or both. Accordingly, it was found necessary to make analyses based on these features. The following tables give the available data furnished by this series of cases in respect to both the size and the number of pancreatic islets in a standard area (tables 7–12). Although the complete series is made up of 202 cases, all necessary details are available in 197, of which 47 are diabetics. The following tables are based, therefore, on the findings in 150 nondiabetics and 47 diabetics. The size of the average islet is measured in planimeter units (P.U.).

Nondiabetics. The group of nondiabetics is sufficiently large to give some idea as to the size and the number of islets in a normal pancreas.

TABLE 6. COMPARISON OF ARITHMETIC AVERAGE OF ISLET AREA READINGS PER FIELD IN VARIOUS DISEASE GROUPS

Disease Groups	Islet Area Reading Over %	No. of Cases
Acute disease	1.6	23
Infants under 1 year	2.5	21
Aplastic anemia	1.9	4
Blood diseases	2.8	13
Malignant disease	3.1	14
Tuberculosis	3.2	14
Syphilis	3.3	3
Chronic diseases	3.1	42

A. Under 10 years of age (10% of nondiabetics). All except 2 of the 30 cases under 10 years of age had 50 or more islets in 10 fields; 20 of the 21 cases under one year belonged to this group (table 7). The average size of islets was between 0.2 and 0.4 P.U. except in 4 cases. There was none over 0.6 P.U., that is, of the enlarged type (table 10).

B. Over 10 years of age (80% of nondiabetics). In direct contrast with the foregoing are those groups of cases over 10 years of age. Fifty-one per cent had between 20 and 50 islets in 10 microscopic fields, while

TABLE 7. ANALYSIS OF 150 NONDIABETICS ACCORDING TO AGE GROUPS AND THE NUMBER OF ISLETS IN 10 MICROSCOPIC FIELDS

No. of Islets in 10 Fields	Age Groups in Years										Total	%
	0–1	1–3	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+		
10– 19								1			1	1
20– 29				1	1	4	3	6	0	1	16	11
30– 39				4	7	2	4	7	6	0	30	20
40– 49	1	0	2	2	4	2	8	5	6	1	30	20
50– 59	4	0	5	1	2	0	2	4	4	0	18	12
60– 69	5	2	7	0	0	2	6	4	1	1	21	14
70– 79	4	0	4	0	1	0	1	2	3	0	11	7
80– 89	1	1	2	0	0	0	2	0		0	4	3
90– 99	1	0	2	0	0	1	0	0	0	0	3	2
100–199	4	0	6	2	0	0	3	2	0	0	13	9
200–299	1	1	2	0	0	0	0	0	0	0	2	1
300–399	0	0	0	0	0	0	0	0	1	0	1	1
Totals	21	4	30	10	15	11	29	31	21	3	150	100

a further 37 per cent were dispersed among the higher groups (table 7). The size of the average islets in over 40 per cent of the cases was between 0.4 and 0.6 P.U. while a further 26 per cent was in the 0.3 P.U. section (table 10).

It seems, therefore, that among the nondiabetics as a whole there are two distinct standards, the one for children under 10, and the other for the higher age groups.

The above data disclose these further points. In 11 per cent of the cases in the nondiabetic group the average size of islets was definitely above the normal range (over 0.7 P.U., table 10), and with the exception of one case these were all over 20 years of age. Furthermore, enlarged islets were present in all adult age groups, in contrast with the diabetics in whom essentially enlarged islets are found in cases over 40 years of age (table 11).

Disease Groups

Diabetes mellitus (*47 cases*). Seventy-six per cent of the 47 cases of diabetes mellitus had from 10 to 30 islets in 10 fields (table 8) while in 81 per cent the average islets measured from 0.1 to 0.6 P.U. (table 11). Six per cent had average islets between 0.1 and 0.19 P.U., a range exclusively limited to diabetic cases. In 19 per cent the average islets were from 0.6 to 1.0 P.U. and these were chiefly cases over 50 years of age.

Thus, in diabetics, normal sized and small islets are common. The incidence of enlarged islets is no greater than among nondiabetics although in diabetics

TABLE 8. ANALYSIS OF 47 DIABETICS ACCORDING TO AGE GROUPS AND THE NUMBER OF ISLETS IN 10 MICROSCOPIC FIELDS

No. of Islets in 10 Fields	Age Groups in Years								Total	%
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+		
10–19	0	0	5	3	2	3	3	2	18	38
20–29	1	0	5	4	2	2	3	1	18	38
30–39	0	0	1	0	2	1	2	0	6	13
40–49	0	0	1	0	0	1	0	0	2	4
50–59	0	0	0	0	0	1	2		3	7
Totals	1	0	12	7	6	8	10	3	47	100

TABLE 9. ANALYSIS OF A NUMBER OF DISEASE GROUPS AND ISLET AREA GROUPS ACCORDING TO THE NUMBER OF ISLETS IN 10 MICROSCOPIC FIELDS

No. of Islets in 10 Fields	Acute Diseases	Aplastic anemia	Malignant Disease	Tuberculosis	Blood Disease	Syphilis	Non-diabetics under 0.9%	Cases 3.6–4.6%	Cases 4.6–5.5%	Cases over 5.5%
20– 29	7	1	1	1	0	0	3	0	0	0
30– 39	6	1	3	3	3	0	1	0	1	0
40– 49	7*	2	0	3	4	0	0	0	0	0
50– 59	2	0	4	2	1	0	0	0	1	0
60– 69	1*	0	3	0	2	0	0	1	2	0
70– 79		0	1	1	1	2	0	3	0	0
80– 89		0	0	1*	1	0	0	0	0	1
90– 99		0	0	0	0	0	0	0	0	0
100–199		0	2*	2*	1*	1	0	3**	2*	3*
200–299		0	0	0	0	0	0	0	0	2**
300–399		0	0	1	0	0	0	0	0	1
Totals	23	4	14	14	13	3	4	7	6	7

Each * denotes a case under 10 years of age.

TABLE 10. AN ANALYSIS OF 150 NONDIABETICS ACCORDING TO AGE GROUPS AND AVERAGE SIZE OF ISLETS IN P.U.

Av. Size of Islet, P.U.	Age Groups in Years										Total	%
	0–1	1–3	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+		
0.10–0.19	0	0	0	0	0	0	0	0	0	0	0	0
0.20–0.29	10	2	12	0	2	1	1	2	1	0	19	13
0.30–0.39	7	2	14	3	2	1	8	8	2	0	39	26
0.40–0.49	3	0	3	3	1	3	8	8	6	0	32	21
0.50–0.59	1	0	1	3	6	2	4	8	7	3	34	22
0.60–0.69	0	0	0	0	1	2	2	1	4	0	11	
0.70–0.79	0	0	0	0	0	1	3	3	0	0	7	
0.80–0.89	0	0	0	0	1	1	2	0	1	0	5	18
0.90–0.99	0	0	0	1	2	0	1	0	0	0	4	
1.0+	0	0	0	0	0	0	0	1	0	0	1	
Totals	21	4	30	10	15	11	29	31	21	3	150	100

TABLE 11. ANALYSIS OF 47 DIABETICS ACCORDING TO AGE GROUPS AND AVERAGE SIZE OF ISLETS IN P.U.

Size of Islet, P.U.	Age Groups in Years								Total	%
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+		
.1–.19	0	0	0	1	0	0	1	1	3	6
.2–.29	1	0	3	3	0	0	1	0	8	17
.3–.39	0	0	1	1	1	2	2	1	8	17
.4–.49	0	0	4	1	1	1	0	0	7	15
.5–.59	0	0	3	0	3	3	2	1	12	26
.6–.69	0	0	1	1	0	1	2	0	5	11
.7–.79	0	0	0	0	1	0	0	0	1	2
.8–.89	0	0	0	0	0	1	1	0	2	4
.9–.99	0	0	0	0	0	0	1	0	1	2
Totals	1	0	12	7	6	8	10	3	47	100

the enlarged islets occur chiefly in cases over 50 years of age, in contrast with the nondiabetics among whom enlarged islets occur in all adult age groups.

It is clear, then, that in diabetes mellitus the reduction in the amount of islet tissue is largely the result of a reduction in the number of islets.

Malignant disease (*14 cases*); *tuberculosis* (*14 cases*); *blood diseases* (*13 cases*); *syphilis* (*3 cases*). Of the total of 44 cases making up the above disease groups, 26 (59%) had over 50 islets in 10 microscopic fields, a frequency about 4 times as great as in acute diseases (table 9). The 4 cases under 10 years of age each had over 80 islets in 10 fields.

The size of the average islets was over 0.6 P.U. in 13 of the 44 cases (25.5%, table 12) as compared with 16.7 per cent in acute diseases (table 10). All cases under 10 years of age had average islets under 0.6 P.U. in size.

TABLE 12. ANALYSIS OF A NUMBER OF DISEASE GROUPS AND ISLET AREA GROUPS ACCORDING TO AVERAGE SIZE OF ISLETS IN P.U.

Av. Size of Islets, P.U.	Acute diseases	Aplastic anemia	Malignant disease	Tuberculosis	Blood diseases	Syphilis	Nondiabetics under 0.9%	3.6 to 4.6%	4.6 to 5.5%	over 5.5%
0.1–0.19	0	0	0	0	0	0	0	0	0	0
0.2–0.29	2*	0	0	0	0	0	2	1*	0	1*
0.3–0.39	7*	1	3	4**	2*	2	2	2*	0	1*
0.4–0.49	5	1	2*	4	1	0	0	0	2*	3*
0.5–0.59	5	0	5	4	4	0	0	1	0	0
0.6–0.69	1	1	2	1	3	1	0	3	0	0
0.7–0.79	1	0	1	0	2	0	0	0	0	1
0.8–0.89	1	1	0	0	1	0	0	0	1	1
0.9–0.99	1	0	0	1	0	0	0	0	2	0
1.0+over		0	1	0	0	0	0	0	1	0
Totals	23	4	14	14	13	3	4	7	6	7

Each * denotes a case under 10 years of age

The indications are, therefore, that the increased islet tissue content in these disease groups is due to an increase both in the number and in the size of the islets. Those under 10 years of age (4 cases) had numerous islets which were within the normal limits as to size.

Cases with Islet Area Readings per Field of 3.6 per cent and Over

All but one of these 20 cases had islet counts of over 50 to 10 microscopic fields, while the 6 cases under 10 years of age had over 100 islets each (table 9). The average size in 9 cases (45%) was over 0.6 P.U. (table 12); the remaining 11 cases, including 6 under 10 years of age, were under 0.6 P.U.

TABLE 13. NUMBER AND SIZE OF ISLETS IN VARIOUS GROUPS

Group	No. of Islets in 10 Fields	Size of Average Islets, P.U.
Nondiabetics under 10 years	50 and over	0.2 to 0.4 none>0.6
Nondiabetics over 10 years	20 to 50 (30% in higher groups)	0.3 to 0.6 (19%>0.6)
Acute diseases	20 to 50	0.3 to 0.6
Diabetes mellitus	10 to 30	0.1 to 0.6
Malignant disease, tuberculosis, blood diseases, syphilis	20 to 50, 41% over 50, 49%	0.3 to 0.6
Cases with islet area readings of 3.6% and over	*a*) over 10 yr., >50 *b*) under 10 yr., >100	*a*) >0.6 *b*) <0.6

These results show that the higher islet area readings are generally associated with an increased number of islets, especially in children under 10 years of age. In adults, however, the increase may be due to enlarged islets. On the whole, therefore, children have a greater number of islets than adults but the average size is less.

The data resulting from the various analyses of the cases according to the number and the size of the islets are summarized in table 13.

DISCUSSION

The main problems connected with this investigation are *a*), those concerned with the establishment of normal standards, and *b*), those associated with the changes in the islet tissue content in disease. The work of Ogilvie has a direct bearing on the points raised under the first heading, while the data available for the second section are provided by the present series.

Normal standards. Ogilvie, in his series, had apparently selected his cases to cover the whole age range; he did not consider the possibility of any alteration in the islet tissue content as the result of disease. Since the present series is essentially of an unselected character, the results lend themselves both to age and sex analyses as well as to the study of any reaction the islet tissue content may have to disease.

TABLE 14. OGILVIE'S SERIES ON ISLET AREA IN PANCREATIC TISSUE

Islet area groups, %	Age Groups in Years											
	Under 1	1	2	Total under 3	0–9	10–19	20–29	30–39	40–49	50–59	60–69	Total
under .9	0	0	0	0	0	0	1	0	3	0	0	4
.9–1.7	0	0	1	1	4	12	7	3	1	4	2	33
1.8–2.6	5	2	0	7	11	5	3	1	5	2	0	27
2.7–3.5	6	7	2	15	15	1	1	0	0	1	0	18
3.6–4.5	5	0	0	5	6	0	0	0	0	0	0	6
4.6–5.5	7	2	1	10	10	0	0	0	0	0	0	10
over 5.5	1	1	0	2	2	0	0	0	0	0	0	2
Total	24	12	4	40	48	18	12	4	9	7	2	100

Both series are subjected to similar analyses in tables 14 and 15. Ogilvie's results have been converted into percentage readings in order to make a direct comparison possible.

If the *0.9 per cent group* can be excluded as diabetics and potential diabetics, then the *0.9, 1.8* and *2.7 per cent groups* include the greater part of both series, i.e. 74.5 per cent of the present series (table 15) and 78 per cent of the Ogilvie series (table 14). Those groups constitute the normal range previously referred to. In both series, too, the figures for these groups correspond both individually and collectively.

Among the infants the Ogilvie series shows quite definitely that there is a tendency for the islet area readings to be higher than in adults. In his complete series including both infants and adults there were 36 cases with readings of 2.6 per cent and over. Of these, 32 were infants and this was four-fifths of the total number of infant cases in the series. Furthermore, among the still higher readings the infant predominance is even more striking. Of the 18 cases over 3.6 per cent only one was not an infant and this one was under 10 years of age.

In the present series the higher readings (over 3.6%) occur to a great extent among the infants under 3, and then with decreasing incidence up to 20 years of age. This corresponds with the findings in Ogilvie's series although in his cases the proportion of higher readings was greater. A further difference in the findings of the two investigations is that although the higher readings in Ogilvie's series are restricted to the infant group, similar readings were found in the present series in 12 cases over 40 years of age or 6 per cent of the whole series. Thus the figures indicate that a high islet tissue content may be *a*), of congenital origin, which as a rule disappears by 20 years of age, or *b*), of an adult type which makes its appearance after 40 years of age.

Ogilvie's data lead him to conclude that during the first year of life the amount of islet tissue is augmented by an increase in the number of islets; then hyperplasia sets in, and by the third year both processes are at work at about the same rate. During childhood and adolescence any increase in the amount of islet tissue is through hypertrophy. At 21 years of age the islet tissue content has become established. These conclusions of Ogilvie conform with the findings of the present investigation.

However, the high islet tissue content in cases over 40 years of age has still to be explained. This was not a feature of Ogilvie's cases but did occur quite definitely in the present series and will be considered at a later stage in this report.

Variations of islet tissue content due to disease.

TABLE 15. ISLET AREA IN PANCREAS IN PRESENT SERIES

Islet Area Groups %	Age Groups in Years														Totals
	Under 1	1	2	Total under 3	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+	Age unknown	Age or sex unknown	
under 0.9	0	0	0	0	1	0	9	6	2	5	5	3	0	2	33
0.9–1.7	7	2	0	9	11	5	7	7	12	18	8	1	0	2	71
1.8–2.6	7	0	0	7	7	2	8	3	10	7	14	1	1	0	53
2.7–3.5	3	1	0	4	6	1	3	2	6	5	1	1	0	0	25
3.6–4.5	1	0	0	1	2	1	0	0	1	2	1	0	0	0	7
4.6–5.5	1	0	0	1	1	1	0	0	2	1	1	0	0	0	6
over 5.5	2	1	0	3	3	0	0	0	2	1	1	0	0	0	7
Totals	21	4	0	25	31	10	27	18	35	39	31	6	1	4	202

Diabetes mellitus in all of its phases is too familiar to require any discussion here. However, hypoglycemia or hyperinsulinism is not so well known and hence a summary of the literature on this condition may be of assistance. The subject has been reviewed by Gammon and Tenery (3), and Wauchope (4).

Harris (5) examined the fasting blood sugar in 1,497 cases and found 67 in whom the level was 0.079 per cent or under. Most of these patients, especially those with blood sugar below 0.069 per cent had symptoms attributable to hypoglycemia. As a result of this study he concluded that mild hypoglycemia was not rare. Later he found among 2541 nondiabetics 218 with various degrees of hypoglycemia including 86 with unmistakable symptoms of the condition (6). The experience of Sippe and Bostock (7) was that in a mixed series of cases the proportion showing hypoglycemia was 0.47 per cent. In the same series there were 0.51 per cent of diabetics. They concluded that hypoglycemia was as common as hyperglycemia.

Diabetics may develop hypoglycemia at a late stage, and this may appear in cases that have not received insulin treatment as well as in those that have. This has been reported by Jonas (8), Joslin (9) and Ashe et al. (10). Hypoglycemia in this form has been termed dyinsulinism.

The age and sex incidence of hypoglycemia also has its interesting features. The 30 to 50-year age groups are most affected but the condition may appear at any age. It is reported to be twice as common in men.

In children hypoglycemia also is a problem. Wauchope (4) found the blood sugar in those under 3 years of age lower than in adults. According to Harris (6) newly born infants of diabetic mothers may die of hypoglycemia; in such cases the pancreas apparently had been overactive in order to compensate for the lack of insulin in the mother. In consequence, the infant at birth develops hypoglycemia. But hypoglycemia may also occur in infants born of nondiabetic mothers (11).

Little can be said concerning the pathology of hyperinsulinism except that numerous workers have reported the presence of hypertrophy and hyperplasia, and, in some cases, adenomata of the islet tissue, while in a few cases the causal lesion was a carcinoma of islet origin.

It is evident, therefore, that conditions exist in which structural features in the islets correspond on the one hand, with underactivity (hypoinsulinism), and, on the other hand, with overactivity (hyperinsulinism); these conditions can be determined to a large extent by ascertaining the proportion of the

DETAILS OF CASES ILLUSTRATED IN DIAGRAMS (FIG. 1 to 21)

Fig.	Case	Sex and age	Disease	Islet area %	No. of islets in 10 fields	Remarks
1	16	M, 43	Acute pericarditis	1.3	40	Normal
2	37	M, 59	Dislocated vertebrae	1.8	53	
3	386	M, 58	Adrenal atrophy Acute pericarditis	0.7	22	Nondiabetic with reading under 0.9%
4	205	F, 7	Chloroma	3.7	131	Nondiabetics with readings of 3.6 to 4.6%
5	28	M, 66	Pulmonary tuberculosis	4.4	71	
6	188	M, 6 mo.	Lymphosarcoma, bronchopneumonia,	4.7	119	Nondiabetics with readings of 4.6 to 5.5%
7	211	F, 43	Otitis media, cerebral abscess, pyemia	4.9	61	
8	31	M, 12	Tuberc. spine, tuberc. bronchopneumonia	5.2	140	
9	91	M, 56	Pellagra, carcinoma of tongue	7.8	123	Nondiabetics with readings of 5.5% and over
10	329	M, 3 mo.	Cerebrospinal meningitis	5.5	135	
11	256	F, 24	Diabetes mellitus	0.7	18	Diabetics with readings under 0.9%
12	364	M, 63	Diabetes mellitus	0.8	18	
13	365	M, 55	Diabetes mellitus, coronary atheroma	0.6	13	
14	224	F, 73	Diabetes mellitus, ulcerative colitis	0.5	10	
15	5		Diabetes mellitus	0.2	22	
16	29	M, 65	Hemochromatosis	0.2	10	
17	237	F, 54	Diabetes mellitus	1.6	21	Diabetics with readings between 0.9 and 1.8%
18	378	F, 54	Diabetes mellitus, chronic gastric ulcer	1.0	36	
19	142	M, 49	Diabetes mellitus	0.9	32	
20	376	M, 62	Diabetes mellitus, pyemia, chronic Pb poisoning,	4.6	55	Diabetics with readings of 1.8% and over
21	299	F, 57	Diabetes mellitus	2.9	48	

islet tissue present. Although this series contains a group of diabetics to illustrate underactivity of islet tissue it does not include any authenticated cases of hyperinsulinism. However, the readings at the upper extreme are sufficiently high to suggest an islet tissue content greater than the normal. A low islet tissue content occurred in very few nondiabetics of both series. Ogilvie in his series of 100 normal cases had only 4 in the 0.9 per cent group. In the present series a similar group was made up of 29 diabetics and 4 nondiabetics, which appears to confirm the view that an islet tissue content of less than 1 per cent is below normal and is significant of diabetes mellitus.

As the diabetic group contained 22 cases with readings over 0.9 per cent, the complete picture is more complicated than is implied by a low islet reading alone; in consequence the group requires further study. At this stage bar diagrams were found to be a useful form of analysis.

The bar diagrams were made by plotting the 10 individual readings for each case (abscissae) against planimeter units as the vertical measure (ordinates). The diagrams for the group of acute cases (fig. 1 and 2) serve as normals. In them there is as a rule a general increase in the height of the columns, although in a few instances the rise tends to be rather sharp. In general the appearances seem to be analogous to those in a normal incidence curve.

An examination of the bar diagrams of the diabetic group with readings under 0.9 per cent discloses that there are three types. A) There are those in which all the columns are very low (fig. 13–16) implying low readings throughout and therefore extensive and uniform islet damage. B) There are those in which low columns are associated with one or several peaks (fig. 12). In these cases islet damage had been followed by some measure of repair either by an increase in the number or the size of the islets, which in turn has given rise to the higher reading. C) There are those which show a reduced normal diagram indicating a uniform reduction of the islet tissue best explained by the assumption of a generalized islet atrophy (fig. 11). In brief, then, the above types represent cases in which there had been extensive

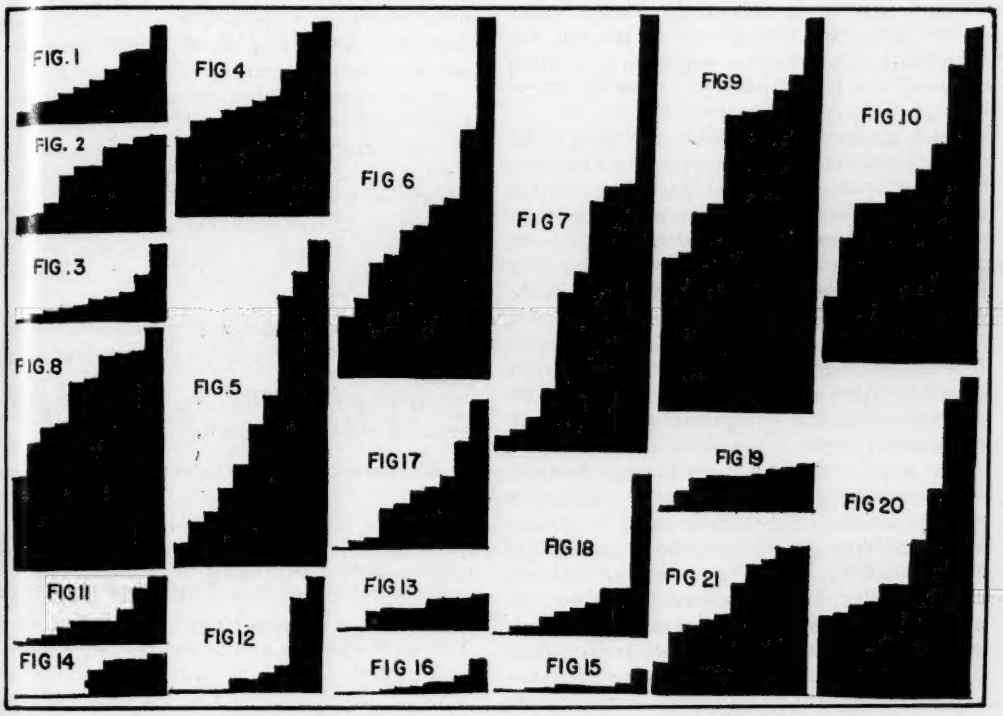

Fig. 1–10. Bar diagrams of general group readings of islet tissue. Each figure represents 1 case consisting of islet area readings in 10 fields (abscissae); the ordinate values represent 0.5 planimeter units converted into percentage of pancreatic tissue. Fig. 1–3, readings less than 0.9%; fig. 4 and 5, readings from 3.6 to 4.6%; fig. 6–8, readings 4.6 to 5.5%; fig. 9 and 10, readings over 5.5%.

Fig. 11–21. Bar diagrams of diabetic group readings; see legend for fig. 1–10. Fig. 11–16 readings under 0.9%; fig. 17–19, readings 0.9 to 1.8%; fig. 20–21, readings over 1.8%.

islet tissue damage with or without repair of a compensatory type, and a separate group in which the low islet tissue content was due to uniform islet atrophy.

In the diabetic group of 0.9 to 1.8 per cent the bar diagrams are mostly of the normal type (fig. 17). A number, however, show the steep upward trend suggestive of compensatory repair (fig. 18). In some the diagrams are in the form of a plateau (fig. 19); this could be explained by the assumption that regeneration had occurred throughout. Those cases in the diabetic group with readings over 1.8 per cent, had exaggerated normal diagrams suggestive of a general hypertrophy or hyperplasia of islet tissue (fig. 20 and 21).

But it must not be lost sight of that many of the diabetics with readings over 0.9 per cent show some degree of hydropic or hyalin degeneration of the islets; such areas cannot be excluded in making the area measurements as they frequently occur in scattered patches within the islets. It is clear therefore that a mere increase in the islet area cannot be the sole criterion of the effectiveness of that islet.

The 4 nondiabetics with readings under 0.9 per cent had bar diagrams which were of the miniature normal type and similar to a form seen among the diabetics (fig. 3); this was assumed to be significant of a uniform atrophy of the islets.

The groups with high islet tissue content have still to be considered. Table 5 shows that the higher readings occurred chiefly in males (males 15; females 5), and in addition to infants, adults over 40 years had a high incidence. This is in accordance with the clinical experience of hypoglycemia. The bar diagrams of all groups with readings over 3.6 per cent, with the exception of 3 cases, show an exaggerated normal appearance (fig. 4–10), and therefore represent either hypertrophy or hyperplasia of the islets in general, or an increased number of islets, rather than compensatory repair following islet damage.

In this series there were no authenticated cases of hypoglycemia but any of the 20 cases with readings over 3.6 per cent might have been potential or possibly actual cases of hypoglycemia, especially since various workers have found that hypoglycemia is as common as hyperglycemia or diabetes mellitus.

CONCLUSIONS

In sections of the pancreas in 202 cases including 51 diabetics, the islets in each of 10 microscopic fields were drawn by a camera lucida, and their total islet area was estimated by a planimeter. The results, in percentage of islet to pancreatic tissue, were analyzed to find out if age, sex, or disease were associated with variations in the total islet tissue content, or in the size or number of islets.

At the one extreme are cases with low islet tissue content and these are almost exclusively diabetics. At the other extreme are those with a high proportion of islet tissue, and the latter were principally infants, or adults with chronic or proliferative diseases.

Under 0.9 per cent of islet tissue is presumably significant of a deficiency of insulin secretion since it occurs in the great majority of cases of diabetes mellitus.

From 0.9 to 2.7 per cent may be considered normal for adults, and from 0.9 to 3.6 per cent normal for infants.

Over 3.6 per cent is classed as high and probably significant of potential or actual hypoglycemia.

I am grateful to Professor Baker for his interest and helpful criticism.

REFERENCES

1. Heilberg, K. A.: *Anat Anz.* 29: 49. 1906.
2. Ogilvie, R. F.: *Quart. J. Med. N. S.* 6: 287. 1937.
3. Gammon, G. D., and W. C. Tenery: *Arch. Int. Med.* 47: 829. 1931.
4. Wauchope, G. M.: *Quart. J. Med. N. S.* 2: 117. 1933.
5. Haris, S.: *Endocrinology* 16: 29. 1932; *Internat. Clin. Series* 42.1: 9. 1932.
6. Harris, S.: *J. A. M. A.* 101: 1958. 1933.
7. Sippe, C., and J. Bostock: *M. J. Australie* 1: 207. 1933.
8. Jonas, L.: Med. Clin. North America 8: 949. 1924.
9. Joslin, E. P.: The treatment of diabetes mellitus. Ed. 4. Lea & Febiger, Philadelphia.
10. Ashe, B. L., H. O. Mosenthal and G. Ginsberg: *J. Lab. & Clin. Med.* 13: 109. 1927.
11. Rascoff, H., J. S. Beilly and M. Jacobi: *Am. J. Dis. Child.* 55: 330. 1938.

Clinical Studies with Male Hormone

V. Therapeutic Use of Pellets of Testosterone Propionate

[Pellet Implantation]

JOHN EAGER HOWARD, M.D., AND HUGH J. JEWETT, M.D.

From the Department of Medicine and the James Buchanan Brady Urological Institute, The Johns Hopkins University and Hospital, Baltimore, Maryland

ADMINISTRATION OF HORMONES by the implantation of compressed pellets of the pure substances has been practiced extensively since the introduction of this technique by Deanesly in 1937 (1). Pellets of desoxycorticosterone acetate have been carefully studied by Thorn and his collaborators and their therapeutic usefulness in patients suffering from Addison's disease has been established (2, 3, 4).

Although the experimental use of androgenic sterols in patients was begun even before desoxycorticosterone was available, the therapeutic use of pellets of testosterone derivatives in patients suffering with androgen deficiency is by no means established on a sure foundation. For this delay there are several reasons.

There has not yet been evolved any standardization of dosage of androgenic substances in any of the techniques of administration. The criteria of adequate and optimal therapeutic effect are matters on which workers in this field have not reached a uniformity of opinion (5, 6). One great difficulty lies in the fact that the metabolic responses to androgenic compounds cannot be measured quantitatively as well as the response to adrenal cortical compounds, and accordingly one must depend on clinical (and often subjective) signs which cannot be assayed accurately.

Pellets of androgenic compounds made by hand lack uniformity in size and consistency, and have given discordant results in the hands of different investigators (vide infra). Androgenic pellets also have a greater tendency to slough than do pellets of desoxycorticosterone compounds, probably due to a more vigorous foreign body reaction (5, 6, 7). It perhaps should be reëmphasized that in no instance have we found infection to play a rôle in sloughing the pellets.

It has been difficult to find patients willing to return at frequent intervals for surgical removal of pellets, so that they may be weighed and the rate of absorption of the material determined. Many of the patients live considerable distances from Baltimore and most of them are regularly employed. Furthermore, the search for the pellets several months after implantation is not always easy, and the probing required to find them is sometimes associated with considerable pain. Often in the surgical removal of pellets for assay, small pieces of the pellets are chipped off, thus rendering them valueless for weight assay.

The absorption curves for pellets of androgens have been studied rather extensively in animals. Most of the reports, however, are concerned with small pellets weighing only 10 mg. or less. Forbes (9) reviewed the literature on the subject and reported his own extensive experiments on the absorption rate of small pellets in the rat. He found that small pellets of testosterone, methyl testosterone and testosterone monopropionate were absorbed on a linear curve (this curve showed the percentage loss per day of each pellet), and he concluded that "such pellets should supply roughly (although not exactly) the same amount of hormone daily until the pellet is about 90% absorbed." Vest, Drew, and Langworthy (10) implanted considerably larger pellets (weighing 300–350 mg. each) in macaques and removed them later for assay. All of the workers with androgen implants in animals have agreed that *a*) the absorption rate probably varies with the surface area of the pellet rather than with its weight, *b*) that the density of the pellet is an important factor in the absorption rate, and *c*) that testosterone, methyl testosterone, testosterone monopropionate and testosterone dipropionate are absorbed in descending order of rapidity.

Only a few reports on the use of androgen pellets in man have come to our attention. In 1939 Howard and Vest (8) reported the successful use of large pellets of testosterone in hypogonad patients. The same authors in the same year also reported successful pellet implantations with the use of an 'injector' instrument (7). Biskind, Escamilla and Lisser (11) implanted many small pellets of methyl testosterone in a series of hypogonad patients. Their pellets varied from 80 to 180 mg. Judged by the subjective effect, these pellets were therapeutically satisfactory for periods of 33

Received for publication November 3, 1941.

TABLE 1. ABSORPTION RATE FROM TESTOSTERONE PROPIONATE PELLETS IMPLANTED IN THE INFRASCAPULAR REGION

Patient	Implantation Date	Removal Date	Weights	Days	Average per Day
			mg.		*mg.*
W.E.P.	5/17/40	3/12/41	63	300	0.46
			29		0.57
			20		0.60
			40		0.53
B. R.	7/19/40	1/ 8/41	42	174	0.91
			48		0.87
S. J.	6/10/40	9/27/40	90	109	1.00
I. W.	4/10/40	11/14/40	50	218	0.70
D. M.	10/ 5/40	4/ 8/41	70	185	0.70
			93		0.58
			90		0.59
			65		0.73
J. H.	6/ 2/41	9/ 9/41	120	99	0.83
S. J.	9/27/40	4/16/41	70	201	0.65
W. G.	9/25/40	*	134	77	0.85
			114	127	0.68
			117	137	0.60
J. R.	4/10/40	2/ 1/41	56	296	0.50
R. E.	5/ 1/40	6/13/41	35	408[1]	0.40
			38		0.40
			39		0.40
			26		0.43
W. A.	5/ 1/40	6/18/41	12	413[1]	0.46
R. H.	7/17/40	11/ 6/40	107	112[2]	0.83
			97		0.92
			110		0.80
			110		0.80
B. H.	9/ 3/41	9/11/41	181	8	2.40
		9/17/41	179	14	1.50
		9/24/41	175	21	1.19
		9/30/41	172	27	1.03
R. C.	9/18/41	9/25/41	178	7	3.10
		10/ 2/41	183	14	1.18
		10/ 9/41	174	21	1.25
A. S.	12/13/40	10/17/41	35	307	0.50

[1] Subjectively, therapy considered inadequate for 3 months.
[2] Subjectively, therapy considered inadequate for 2 weeks.
* Sloughed on 12/11/40, 1/30/41 and 2/9/41.

to 79 days. Dorfman and Hamilton (12) implanted pellets of 10 mg. each on two occasions, once the total dosage being 90 mg. and again 280 mg. There was not entirely satisfactory clinical response (subjective) in either case. In a very recent paper Escamilla and Lisser (13) reported on the clinical use of larger pellets each weighing 200 mg. In one patient 4 pellets of methyl testosterone totaling 800 mg. proved subjectively adequate for 3½ months. The pellets were removed after 4 months and had lost per day an average of 3.5 mg. or not quite 0.87 per pellet per day. In another case 3 pellets of methyl testosterone were implanted and proved effective for only 11 weeks. In the third case in which they used 200 mg. pellets, 800 mg. was implanted. The patient was lost sight of two months later at which time the implantation seemed to be subjectively adequate.

METHODS

The primary object of this article is to report observations on the absorption of pellets of testosterone propionate. All pellets used in this series were machine-made under uniform aseptic conditions and they weighed approximately 200 mg.[1] Because of the possibility of bacterial contamination we have not weighed the pellets prior to implantation. Ten pellets, however, were picked at random by the manufacturers from a large lot and their weights were found to vary from 207.8 to 200.2 mg. The mean weight of these ten pellets was 202.6 mg., and the average deviation from the mean was 1.8 mg. All the pellets were implanted by essentially the same technic as reported previously from this clinic (8) except that the sites in all instances were in the infrascapular region upon the muscle fascia, and each pellet was placed at a distance of approximately 6 cm. from the incision line. A small pocket was made for each pellet by inserting a closed Halsted clamp backward along the fascia from the incision line and then opening the clamp. Into the pocket thus made one pellet was inserted through a nasal speculum, the opening being closed with a single silk suture.

In evaluating the absorption rates of the pellets only those pellets which were removed entirely intact and unchipped are charted. Because of the technical difficulties previously mentioned, it was possible to gain information of use in absorption rates from only 14 of a total series of 22 implantations which were made with this type of pellet.

RESULTS

Absorption curves. The data on the rate of absorption of the surgically removed pellets and those which sloughed are shown in table 1. Since it was felt that the absorption rate from pellets which sloughed might not be the same as if they had remained in situ, the data were not at first included in the charts. Their absorption rate falls closely along the general curve of those pellets surgically removed so it was thought permissible to include them in the series. Figure 1 shows the average loss per day from each pellet plotted against the number of days that the pellet remained in situ.

In the earlier cases the pellets were removed only after prolonged periods of time. It was found that, as

[1] These pellets of testosterone propionate (Perandren) were furnished to us by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

a rule, the longer the pellet had remained the less had been its daily loss. Thus it may be seen that in those instances in which the pellets remained more than 400 days after implantation, the average daily absorption amounted to somewhat less than 0.5 mg. per day for each pellet. In those instances in which the pellets were removed between 180 and 220 days after implantation, the average daily absorption was between 0.6 and 0.75 mg. Because it had been our impression that the thick fibrous capsule which forms around the pellet was largely responsible for the surprising uniformity of the absorption rate, it seemed likely that the rate would be more rapid in the early days after implantation before the capsule had been formed. In two patients it was possible to remove pellets at weekly intervals after implantation. This hypothesis for absorption of pellet material was found to be correct. It can be seen in the figures that in the first week after implantation there was a rapid loss of the pellet's substance with average daily losses far greater than those found later. Furthermore, the variation in absorption rates in these early days is seen to be greater than at later periods. The initial pellet weights are recorded as 200 mg. Since this may vary between 200 and 208 mg., a considerable error is introduced into the calculation of the first week's absorption rate. Since all pellets weighed more than 200 mg., the proportional difference between absorption rate between the first week and succeeding weeks would be even greater than that shown in the figures. A greater variation in absorption rate might be anticipated in the first week since one would expect considerable difference in tissue reactivity (and, hence, rate of capsule formation) from patient to patient.

Therapeutic effectiveness. The difficulties involved in evaluating the therapeutic effectiveness of androgen administration have been discussed (3). As an aid in this evaluation the most striking objective changes in our first group of hypogonad patients treated with 25 mg. of testosterone propionate twice each week were charted. We have termed this chart the primary pattern of response (3). Six of the cases included in this present report had had no androgenic therapy prior to the implantation of the five 200 mg. pellets of testosterone propionate. In all of these six cases the objective response fell well within the limit of, or—in many instances—bettered, our primary pattern. Therefore, the androgenic therapy supplied by the pellets was as good as if not better than that produced by the injection of 25 mg. of testosterone propionate twice each week.

In the eight patients of this group who previously had been given effective androgenic therapy by some other method, the implantation of five 200 mg. pellets maintained or advanced the effects previously obtained.

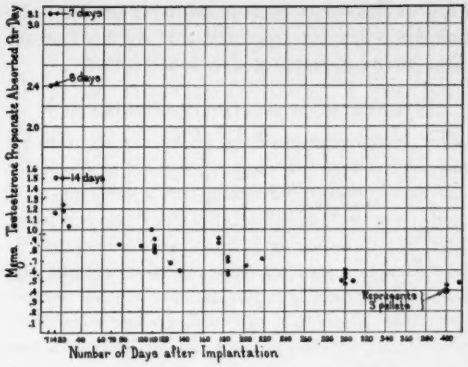

Fig. 1. Each point on the graph represents the amount of the drug absorbed per day from an individual pellet. These figures are calculated by subtracting the weight of the pellet at the time of removal from its initial weight, and dividing by the number of days the pellet remained in situ.

Duration of pellet effects. We have repeatedly emphasized the dangers of relying on subjective criteria in evaluating androgenic therapy (5, 6, 8). However in estimating the effective duration of the pellets in this series of cases, we are compelled to rely on the patients' own evaluations to a considerable extent. We have found, using other methods of administration, that when effective therapy ceases, the patients complain of certain changes in their status which are fairly characteristic. Among these are *a*), the failure of ejaculation, *b*) loss of libido and *c*), a general deterioration in the sense of well being. These symptoms are reported long before we are able to detect any objective regression except a diminution of the amount of prostatic secretion obtained by massage.

Four patients in this series complained that the pellets had become ineffective or, as they expressed it, had "run out" at the time of their removal. Two of these were those in whom the pellets had remained more than 400 days. *Patient W. A.* stated that his treatment had not been "good enough" for about two months; in other words, the 5 pellets had given him subjectively satisfactory response for approximately 350 days. In the case of *Patient R. E.*, the feeling was expressed that he had needed "more stuff" for nearly 4 months prior to the date of pellet removal. Thus, subjectively, the pellet had been adequate for about 290 days. *Patient A. S.* reported at 307 days that the pellets had been "not so good for 7 weeks though they are still working some." *Patient R. H.* felt that the pellets had yielded adequate therapy for only a little over three months and the reason for his return to us on the 112th day was that "the pellets have run out now for about two weeks." All of the other patients in this series felt that for the duration of their implants the therapeutic effects derived were entirely adequate and satisfactory. One other patient, not in-

cluded in this series because we were unable to remove the pellets for assay, felt that the five 200 mg. pellets were adequate for only four months.

INTERPRETATION OF RESULTS AND DISCUSSION

Our interpretation of the above results is as follows. In the first few days after pellet implantation there is a rather rapid absorption amounting to as much as 3 or more milligrams per day from each pellet. After this, presumably with capsule formation, the absorption rate steadies down to a surprisingly constant rate somewhere between 0.5 to 1.0 mg. per day. This daily absorption rate will continue for many days, falling gradually until the pellet has become very small. This is in line with the findings of Forbes in his rat experiments.

Upon many variable factors will depend the amount of androgen required to maintain adequate response in a group of hypogonad patients. It seems unreasonable to suppose that every patient suffering from hypogonadism will require the same daily dose of androgen. Since each pellet in the period between the 15th and the 200th day yields from 0.6 to 0.9 mg. per day, the combined yield of 5 pellets would be between 3 and 4.5 mg. For a patient who requires for adequate subjective effect a minimum of 4 mg. per day 5 pellets would be sufficient for a considerably shorter period of time than would be the case for a patient whose required dosage might be only 3 mg. per day. If this hypothesis is correct, in a patient in whom 5 pellets have become inadequate in 4 or 5 months we should be able to provide an adequate absorption level by implanting 2 more pellets. Then, perhaps, when a new implant is considered, 7 or 8 pellets might be more suitable than 5. It should be stressed that five 200 mg. pellets have been subjectively adequate in all of our patients to date for at least 3 months, and in most patients for longer periods.

From these findings we have concluded that during the first week or so after implantation considerably more androgen is absorbed than is necessary. No harmful results have been noted. It is true in the first week or two of therapy that the previously untreated patients have noted much more vigorous stimulation in the sexual sphere than they have experienced later; nevertheless this same subjective overstimulation has occurred at first in all of our hypogonad patients, with any of the methods of androgen administration we have used. This has been attributed to the hypersensitivity that is commonly seen in endocrine deficiencies to the substance that is lacked.

In this paper we are not concerned with optimal or adequate dosage of androgens. However, it seems from the data presented, that one can readily vary the dosage of testosterone propionate over wide limits as may be desired simply by implanting more or fewer pellets. Our patients who have been treated by pellets, by injection or by oral androgenic therapy have, with a single exception, preferred pellet administration. Other advantages of pellets over intramuscular injection or oral administration of androgens are the great saving of material and the elimination of nuisance to the patient in having to take injections or tablets.

SUMMARY

Our experience with machine-made pellets of testosterone propionate implanted beneath the skin in patients suffering with hypogonadism has been discussed. We have found this method of administration satisfactory; it is the most saving of material and, unless the pellets slough, the least trouble to the patient. Duration of effects is discussed, and charts of absorption rates are given. In some patients a given number of pellets supplies subjectively adequate therapy for only a few months, whereas in others this same dose will be effective for a year or more. We have explained this variation in effect on the theory that the former group of patients requires a higher daily supply for adequate subjective effects than do the latter.

REFERENCES

1. Deanesly, R., and A. S. Parkes: Factors influencing effectiveness of administered hormones. *Proc. Roy. Soc., London, s. B.* 124: 279. 1937.
2. Thorn, G. W., R. P. Howard, K. Emerson, Jr. and W. M. Firor: Treatment of Addison's disease with pellets of crystalline adrenal cortical hormone (synthetic desoxycorticosterone acetate) implanted subcutaneously. *Bull. Johns Hopkins Hosp.* LXIV: 339. 1939.
3. Thorn, G. W., and W. M. Firor: Desoxycorticosterone acetate therapy in Addison's disease. *J.A.M.A.* 114: 2517. 1940.
4. Thorn, G. W.: Treatment of Addison's disease. *J. Clinical Endocrinology* 1: 76. 1941.
5. Howard, J. E.: Chemical, physiological and clinical aspects of the androgens. *Bull. New York Acad. Med.* 17: 519. 1941.
6. Howard, J. E., and H. J. Jewett: Androgens and androgenic therapy. *Bull. Richmond Acad. Med.* 9: 96. 1941.
7. Vest, S. A., and J. E. Howard: Clinical experiments with androgens. IV. A method of implantation of crystalline testosterone. *J.A.M.A.* 113: 1869. 1939.
8. Howard, J. E., and S. A. Vest: Clinical experiments with male sex hormones. II. Further observations on testosterone propionate in adult hypogonadism, and preliminary report on the implantation of testosterone. *Am. J. M. Sc.* 198: 823. 1939.
9. Forbes, T. R.: Absorption of pellets of crystalline testosterone, testosterone propionate, methyl testosterone, progesterone, desoxycorticosterone and stilbestrol implanted in the rat. *Endocrinology* 29: 70. 1941.
10. Vest, S. A., J. E. Drew, and O. R. Langworthy: Some comparative effects of testosterone derivatives in the monkey. *Endocrinology* 28: 257. 1941.
11. Biskind, G. R., R. F. Escamilla and H. Lisser: Implantation of testosterone compounds in cases of male eunuchoidism. *J. Clinical Endocrinology* 1: 38. 1941.
12. Dorfman, R. I., and J. B. Hamilton: Rate of excretion of urinary androgens after administration of testosterone by various routes. *J. Clinical Endocrinology* 1: 359. 1941.
13. Escamilla, R. F., and H. Lisser: Testosterone therapy of eunucoids. II. Clinical comparison of parenteral implantation and oral administration of testosterone compounds in male eunuchoidism. *J. Clinical Endocrinology* 1: 633. 1941.

The Modifying Influence of the Presence of Testicular Tissue on the Efficacy of Testosterone Pellets in the Treatment of the Eunuchoid Patient

[Methyl Testosterone Orally]

ROBERT C. GRAUER, M.D., AND
MAITLAND ALEXANDER, JR., M.D.

From the Department of Research in Endocrinology and Metabolism, William H. Singer Memorial Research Laboratory, and the Allegheny General Hospital, Pittsburgh, Pennsylvania

DIVERSIFIED TYPES of eunuchoid patients were employed in this study in order to learn what influence the presence of testicular tissue had on effective doses of testosterone. Two patients were bilateral cryptorchids, 21 and 33 years of age, in whom no testicular tissue was demonstrable. Two others were 20 and 31 years of age and had undeveloped retractile testes which apparently were either nonfunctioning or which gave evidence of a minimal amount of activity. The fifth patient had had an unilateral orchipexy performed but was deficient in testicular function. The sixth patient exhibited definite hypogenitalism which was associated with a primary gonadotropic pituitary deficiency. Subcutaneous implants of testosterone as a method of treatment in cases of testicular deficiency were introduced experimentally by Deanesly and Parkes (1). Following this, reports of the clinical application of this method of therapy appeared in the literature (2). To be clinically expedient, a mode of therapy should be effective; it should have no undesirable side effects and it is essential that it be reasonably inexpensive and possess ease in administration. In order to determine the best method of fulfilling these criteria, the aforementioned six preadolescent eunuchoid patients were employed in our study. The cryptorchid patients acted as excellent controls for comparison with the patients who possessed some testicular tissue.

METHOD OF STUDY

The study was divided into a clinical and laboratory evaluation, and attempts were made in all cases to integrate the findings by these two methods of approach.

Received for publication November 6, 1941.

Clinical study. General physical examination, basal metabolic rate determinations and roentgenograms of the hands and wrists for the determination of the bone age were made in all cases. Each patient was given an initial subcutaneous implant of 300 mg. of testosterone.[1] The two cryptorchid patients were given a single subsequent implant at an interval of 6 weeks, and following this were given 80 mg. of methyl testosterone by mouth daily. The other four patients received subcutaneous pellet implantations at intervals of 6 to 8 weeks. No oral testosterone was given to these patients. The objective and subjective changes in the patients were recorded before and during the course of the treatment.

Laboratory study. Twenty-four-hour collections of urine were assayed at weekly intervals for three successive weeks preceding the administration of any type of medication. This was done in order to secure an approximate idea of the type of androgenic and estrogenic excretion curves in this type of patient. After the implantation of the testosterone, 24-hour collections of urine were secured at 5 to 7 day intervals for a period of 3 to 8 months. All specimens of urine were assayed for estrogens and for androgens. The latter were determined biologically in accordance with our modification of the chick-comb-weight method (3) and colorimetrically according to the method of Neustadt (4). This was done in order to compare the excretion curves of the biologically active material with the colorimetric measurement of the 17-ketosteroids and to learn whether these curves could

[1] The testosterone pellets and the methyl testosterone that were employed in this study were supplied by the Schering Corporation, Bloomfield, N. J. through the kindness of Dr. Edward Henderson.

indicate the proper dose of testosterone that was to be administered to the patients.

Technique of implantation. Originally, flat pellets (disks) were employed for subcutaneous implantation. This was accomplished through an incision in the skin after preliminary infiltration with 2 per cent novocain. A point was chosen between the seventh and ninth ribs in the midaxillary line. The incision was made in the intercostal space and varied from 1 to 3

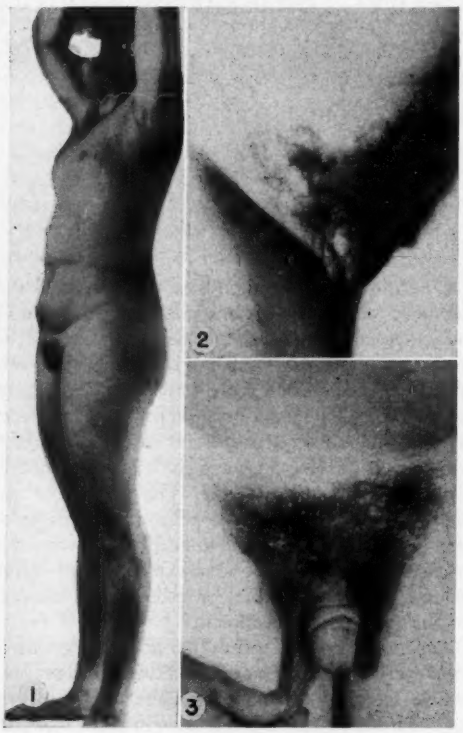

Fig. 1–3. *Patient* W. M. Fig. 1. BEFORE TREATMENT. Notice female configuration of body outline. Age 33 yr. Fig. 2. Close-up shows scars of unsuccessful orchipexy. Observe absence of testes. Fig. 3. After receiving 450 mg. testosterone subcutaneously. Marked and rapid response resulted within 2 months.

inches in length. Small pockets were then made in the subcutaneous tissue and a small nasal speculum was introduced into the pockets thus formed. The disks were slipped into the pockets between the separated blades of the speculum. This gave a comparatively dry field and facilitated introduction of the pellet. Following this earlier method of implantation, it was shown that the immediate rate of absorption of the testosterone depended upon the degree of surface contact which the pellet made with the body fluid (5, 6, 7) rather than upon the mass of the pellet. Consequently the use of cylindrical pellets measuring 3 by 8 mm. was adopted in this work. This type of pellet has since simplified the method of administration. In place of making an incision in the conventional manner, a number 3 trocar with a beveled edge is introduced subcutaneously, after the skin has been infiltrated with 2 per cent novocain. No preliminary nicking of the skin with a scalpel is necessary. Up to 6 or even 8 pellets, each weighing 75 mg., can thus be introduced at one time. No suture is required and a small dry dressing suffices. The advantages of this method of administration immediately become apparent. It is simple, rapid, leaves no scar and facilitates the initial rate of absorption of the testosterone.

CASE HISTORIES

Patient 1, A. C., age 21 years had always suffered from bilateral cryptorchidism. The patient exhibited the findings typical of a pre-adolescent eunuchoid. He measured 73 1/2 inches in height, his span was 78 1/8 inches, and his weight was 181 pounds. His face was smooth and he had never shaved; there was an extremely sparse growth of pubic hair; there was no axillary hair nor hair on his chest. The genitals were small, the penis being infantile in size; the scrotum was flat and resembled labial folds; the prostate was small, being about the size of that of a prepuberal boy. His B. M. R. was −16 per cent. Roentgenograms of the hands and wrists showed failure of epiphyseal closure and the bone age was that of a boy of 14 years, 9 months. The patient had never had erections or nocturnal emissions. On 3/1/41, 300 mg. of testosterone was implanted under the skin. Priapism occurred 3 days after implantation of the pellet. At this time there was also an increased output of urine. On 5/17/41, 300 mg. was again inserted. The penis was definitely increased in size, the prostate was larger and pubic and axillary hair showed rapid growth. On 6/14/41, the patient weighed 200 pounds (a gain of 19 pounds), measured 74 1/2 inches (grew 1 1/4 inches), and his span was 81 inches (2 7/8 inches increase). Beginning 6/21/41, the patient was given daily oral doses of 80 mg. of methyl testosterone. The general improvement continued and the patient began to shave once a week on 8/2/41. On 8/30/41 his B. M. R. was +7 per cent. Acne developed on the face for the first time. This is a common finding when the eunuchoids are given androgenic therapy. On 9/20/41 the patient reported that he was shaving three times a week. His height at this time was 75 inches, and his weight was 215 pounds. There was a complete change psychologically; a previously diffident and sensitive individual became an aggressive and self-confident person. The patient informed the authors that he was contemplating marriage in the very near future. Roentgenograms of the hands and wrists which were taken on 9/14/41 showed no progress in epiphyseal closure, the appearance being the same as at the beginning of treatment.

Patient 2, W. M., age 33 years. This patient was similar in all respects to *patient* A. C. His height was 69 1/2 inches, his span 73 inches, and his weight 202 pounds. He was operated upon on Oct. 17, 1917, for bilateral undescended testes. The testicles were supposed to have been placed in the scrotum, but as far as the patient can recall,

the operation was unsuccessful. Palpation failed to reveal any testicular tissue. The prostate was small and the external genitals were infantile in type. The pubic hair was very sparse, and there was no axillary hair nor hair on the chest. The patient's bone age was that of a boy of 17 years. On 1/27/41, 300 mg. of testosterone was implanted subcutaneously. The patient was not seen again until 5/9/41. At this time the penis had definitely increased in size, there was a heavy growth of pubic hair and an increased growth of axillary hair. The patient stated that potency was present for the first time. On 5/13/41, a 150 mg. pellet was inserted subcutaneously. A smaller dose than the original was found to be sufficient for the patient's needs. On 6/26/41, the patient began receiving 80 mg. of oral methyl testosterone daily. On 8/7/41, a slight acneform eruption appeared on the face and chest. The patient was then shaving once a week, the prostate was definitely increased in size, and his weight had increased to 213 pounds. His B. M. R. was +26 per cent; pulse 82. The hair growth continued to increase and the genitals reached the biological limits of their growth. The patient has been receiving 60 mg. of methyl testosterone daily and up to the present time has shown maintenance of his improved condition.

Patient 3, *A. K.*, age 20. The patient was first seen on 5/7/37, at which time a diagnosis of cryptorchidism due to primary hypopituitarism was made. His height was 60 1/4 inches and his span was 61 1/4 inches. The B. M. R. was +29 per cent. The glucose tolerance curve showed an increased tolerance for sugar, with the greatest rise being .09 per cent. Pregnancy urine extract (200 R.U.) was given three times a week from 6/5/37 to 11/8/37. His height at this time was 61 1/2 inches, span 62 1/4 inches. Both testicles had descended into the scrotum, but there was no increase in the size of the penis nor scrotum. The prostate was small. Anterior-pituitary-like substance was then continued for two months more. The patient's physical condition remained static. Roentgenograms taken on 5/5/38 showed retardation in skeletal development. Urinary assays showed the presence of FSH, yet the patient failed to show any improvement in the size of the penis, scrotum or testicles. There was a very slight growth of pubic hair but no axillary hair. The patient was seen again on 3/7/41 after returning from a C.C.C. camp. His height at this time was 66 1/4 inches and his span was 68 1/4 inches. The genital development was unchanged; the testicles were still in the scrotum but they were only pea-sized and were retractile, slipping into the inguinal canals and giving the appearance of undescended testes. On 4/22/41, 300 mg. of testosterone propionate was implanted subcutaneously. The patient showed very little improvement. On 5/21/41, 300 mg. was again implanted. The scrotum increased in size, the testicles were larger and the penis showed increased growth. The patient was troubled at this time by a mild degree of transient priapism. From this time until 8/7/41, the patient's condition showed no decided improvement. On 8/7/41, 450 mg. of testosterone was inserted subcutaneously. On 9/5/41, 300 mg. was again inserted subcutaneously. A total of 1350 mg. was necessary to bring about improvement in his condition which was comparable to that obtained with 300 mg. of testosterone in the cryptorchid cases. The patient's B. M. R. on 9/5/41 was +6 per cent. His height was 67 3/4 inches, weight 128 pounds. This patient developed an acneform eruption on his face and chest on 9/12/41. His voice became deeper and his skeletal musculature showed increased development.

Patient 4, *J. R.*, age 24 years. The patient had a bilateral congenital inguinal hernia associated with cryptorchidism. At the age of 12 years, an herniotomy and orchipexy were done on the right side; the left side was not corrected. Subsequent to this operation, the testicle on the right side had undergone atrophy. Roentgenograms taken on 9/20/40 and 6/12/41 showed a bone age of 17 years. No progress in epiphyseal closure was observed. The patient was given pregnancy urine extract twice a week for 6 months which resulted in a slight increase in hair growth but no increase in the growth of the genitals. On 10/10/40, the hernia on the left side was corrected and a left orchipexy was performed. A much atrophied left testicle was brought into the scrotum and fixed. Sufficient testicular activity resulted to bring about improvement in the size of the sex organs and to cause a slight increase in hair growth, but this was not sufficient to cause the patient to shave. On 6/12/41, the patient weighed 139 pounds; his height

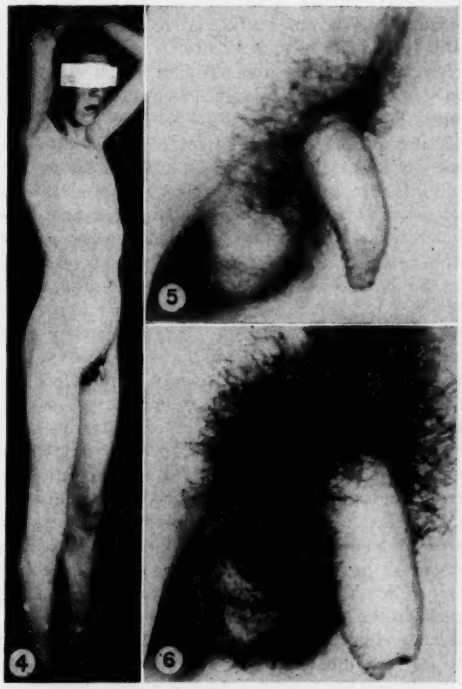

Fig. 4–6. *Patient* A. K. AGE 20 YEARS. Fig. 4. BEFORE TREATMENT. Small undeveloped testes in scrotum. Fig. 5. Close-up showing undeveloped testes. Fig. 6. Total of 1350 mg. of testosterone required over a period of 5 months to produce effect comparable to those in *patient* W. M.

was 72 1/4 inches, and his span was 71 1/4 inches. There was definite bilateral gynecomastia. There was no axillary hair and only a moderate growth of pubic hair. The scrotum was fairly well developed. The right testicle was the size of a hazelnut; the left testicle was about the size of a small pea. His B. M. R. was −21 per cent. A pellet of testosterone weighing 150 mg. was implanted under the skin on 6/12/41. The patient stated that enuresis, which had always been present, stopped completely after insertion of the first pellet. We consider this an extremely significant occurrence. As reported by the other patients, there was an increase in the flow of urine during the day. On 7/24/41, 300 mg. of testosterone was inserted under the skin. The gynecomastia began to recede and on 9/6/41 his B. M. R. was −12 per cent; his height was 72 1/2 inches and his weight 135 pounds. The patient's voice was deeper and he exhibited a marked increase in physical endurance.

Patient 5, J. Y., age 31 years. Chief complaint was sexual underdevelopment. The patient stated that his testicles were undescended. His family history revealed that his two sisters are hypogonadal and of the eunuchoid type. Examination revealed his height to be 69 inches, span 77 inches, and his weight 144 pounds. The penis was infantile, the scrotum was undeveloped and two small, retractile testes, hazelnut in size, could be forced into the scrotum from the inguinal canals. There was a very slight growth of pubic hair and no axillary hair was visible. The patient had never shaved. On 6/14/41, a roentgenogram of the hands and wrists showed failure of epiphyseal closure. In brief, the patient revealed all of the findings of the typical eunuchoid state. A 300 mg. pellet of testosterone was inserted subcutaneously on 6/14/41. The patient experienced priapism for several days following the insertion of the pellet. Six weeks after the insertion of the pellet, there was an increase in the size of the penis and a slight increase in hair growth. No striking changes were observed. On 7/26/41, 300 mg. of testosterone was again inserted. In the succeeding 6 weeks, the patient showed a moderate degree of general improvement. On 8/30/41, 450 mg. was inserted subcutaneously. At this time his B. M. R. was 0. On 9/4/41, his right knee became swollen and edematous but was painless. On 9/20/41, the edema of the right knee disappeared. Roentgenogram examination of his hands and wrists at this time showed it to be the same as on 6/14/41. His weight was 157 pounds (gain of 13 pounds); height 69 1/4 inches (increase of 1/4 inch). There was a marked increase in axillary and pubic hair. The penis was larger. The skin was a darker tan and ruddier. The patient showed an increase in muscular development.

Patient 6, C. S., age 31 years. Patient showed marked obesity, a lack of sexual development, short stature, and failure in facial hair growth. His height was 60 inches; his span was 60 inches, and his weight was 174 pounds. The axillary hair was sparse and there was a slight growth of pubic hair. There were large rolls of abdominal fat and a prominent mons veneris. The penis was infantile, the scrotum was not developed, and the testicles were small, hazelnut in size and retractile. The prostate was prepuberal in type. His B. M. R. was +7 per cent. Roentgenogram examination of the skull showed a sella which was shallow and difficult to visualize. His hands showed complete epiphyseal closure. On 8/12/41, 450 mg. of testosterone was inserted subcutaneously. His primary response was rather delayed, which was similar to that of other patients who had some testicular tissue. On 9/23/41, 300 mg. of testosterone was again inserted subcutaneously. At this time the penis was slightly increased in size and the prostate gland showed a moderate degree of increase.

DISCUSSION

From this study it becomes apparent that the presence of testicular tissue, regardless of the amount, will modify the patient's response to the administration of androgenic substance. When there is complete absence of testicular tissue, as in *patients A. C.* and *W. M.*, the response to treatment is prompt and the amount of material necessary to bring about improvement is minimal. The clinical differences that were observed between these two patients and the four which had a minimal amount of testicular tissue were substantiated in the laboratory by variations in the type of excretion curves that were secured by biological assay as compared to the curves that were secured colorimetrically. This phase of the work is to be discussed in greater detail in a subsequent communication.

It was originally hoped that the excretion curves would be a means whereby the optimum and maintenance doses of testosterone could be determined for each patient, but it was shown in our work that urinary excretion of androgens is no criterion for dosage. This was also suggested by Biskind, et al. (8). It therefore becomes apparent that the clinical response of the patient is the only adequate and practical method for determining the amount of androgenic material to be used and the frequency of its implantation.

The failure of those patients who possessed some testicular tissue to give a maximal early response to the administration of testosterone emphasizes the fact that existing testicular tissue is probably affected by and in turn influences the activity of extraneous androgens. This preparation should not, therefore, be employed in those individuals who do not show a marked anatomical failure in testicular development. This should caution against its promiscuous use. Shay and Gershon-Cohen (9) have shown that testosterone has a depressing influence on the testicles, depending upon the dose that is employed.

We observed that subcutaneous implants of testosterone would stimulate the patient for a period of 6 to 8 weeks. Confirming the observations of Eidelsberg and Ornstein (7), the maximal stimulation occurs during the first month of pellet implantation. This clinical observation is in agreement with the experimental work of Emmens (6) who showed that the rate of ab-

sorption of free testosterone was about 36.8 per cent per month. The second month the total rate of absorption was 87.5 per cent. It was also observed that the initial rate of absorption is greater with cylindrical pellets than with the disk-shaped ones. The latter type of pellet is to be preferred if one wishes to maintain a certain dose level after an initial rapid effect is secured with the cylindrical type. It would therefore appear that a smaller dose of the disk-shaped tablet might be used as a maintenance method of treatment.

The choice between the subcutaneous and the oral method must be determined entirely on a clinical basis. We observed that methyl testosterone by the oral route failed to show the excretion of biologically active androgens in the urine. The interpretation of this phenomenon, from our present knowledge, becomes one of academic importance only. Its significance must await more information concerning the intermediary metabolism of the male sex hormone. Clinical response to testosterone is equally good by the subcutaneous and the oral route. The question of expense is the chief objection to the use of methyl testosterone at the present time. The easy administration of the pellets of free testosterone subcutaneously, by means of the trocar, and the comparatively decreased cost strongly recommend it as the method of choice in the treatment of the eunuchoid state.

The disappearance of enuresis in *patient 4 (J. R.)* lends support to the theory that strengthening of the bladder detrusor musculature is a part of the general skeletal muscular improvement that follows the administration of testosterone. This, according to Kearns (10), may also explain the improved emptying power which follows the use of testosterone in cases of prostatism. Since the depressing influence of testosterone on the testes may be disregarded in cases of prostatism because of the age incidence, it would appear to be well to recommend its use in selected cases of prostatism.

None of our patients showed any tendency toward epiphyseal closure in the hands and wrists at the end of treatment with testosterone. In the female epiphyseal closure has been said to be linked to the production of estrogen but we have not found the same tendency regarding the supply of androgen in the male.

SUMMARY

The presence of testicular tissue in the eunuchoid patient modifies the effectiveness of testosterone. Patients in whom no testicular tissue was demonstrable reacted more readily and required less testosterone than did those in whom some testicular tissue existed. The oral administration of methyl testosterone advanced to the biological limit the anatomical development produced by pellets of subcutaneously implanted testosterone.

Laboratory studies of excretion curves indicate that the clinical response of the patient is the only available criterion for dosage at the present time.

The authors wish to acknowledge the assistance of William F. Starkey, Ph.D., and Eleanor Saier, M.S., during the course of this work.

REFERENCES

1. Deanesly, R., and A. S. Parkes: *Proc. Roy. Soc., London, s.B.* 124: 279. 1937.
2. Howard, J. E., and S. A. Vest: *Am. J. M. Sc.* 198: 823. 1939.
3. Starkey, W. F., R. C. Grauer and E. Saier: *Proc. Soc. Exp. Biol. & Med.* 44: 649. 1940.
4. Neustadt, R.: *Endocrinology* 23: 711. 1938.
5. Kochakian, C. D.: *Endocrinology* 28: 478. 1941.
6. Emmens, C. W.: *Endocrinology* 28: 633. 1941.
7. Eidelsberg, J., and E. A. Ornstein: *J.A.M.A.* 117: 1068. 1941.
8. Biskind, G. R., R. F. Escamilla and H. Lisser: *J. Clinical Endocrinology* 1: 38. 1941.
9. Shay, H., J. Gershon-Cohen, K. E. Paschkis and S. S. Fels: *Endocrinology* 28: 485. 1941.
10. Kearns, W. M.: *J. Clinical Endocrinology* 1: 126. 1941.

Clinical Results Obtained with Sublingual Administration of Methyl Testosterone

[Menopausal Therapy]

CHARLES A. JOËL, M.D.

From the Department of Gynecology
Basle University, Basle, Switzerland

AFTER RUZICKA (1) and his coworkers in 1935 showed that methyl testosterone was one of the potent substances in a series of twenty compounds evaluated by Tschopp's 10-day cock's comb test, the efficacy of the preparation was also estimated by the seminal vesicle test (2). It was found that, whereas quantities of 50, 100 and 200 micrograms of testosterone produced an increase in weight of the seminal vesicles of 40, 70 and 130 mg. respectively, the same amounts of methyl testosterone produced increases of 50, 114 and 140 mg. respectively. Methyl testosterone was shown by Deanesly and Parkes (3) to be appreciably more active than testosterone on the prostate and seminal vesicles of castrated rats but only one-fifth as active in the capon comb test. It is thus seen that methyl testosterone is the most effective of all of the compounds investigated when evaluated by the seminal vesicle test.

Shapiro (4, 5) showed that methyl testosterone in common with certain other steroids may induce ovulation in *Xenopus laevis*, the South African clawed frog. According to Deanesly (6) methyl testosterone implanted subcutaneously in the form of compressed tablets in castrated rabbits produced striking proliferation and growth of the atrophic uterus masculinus.

According to Miescher and Tschopp (7) the methyl derivative retains its activity much better than testosterone when given by mouth to castrated rats. In their experiments castrated rats were given methyl testosterone dissolved in alcohol by means of a stomach tube in daily doses of 1 and 5 mg. for 10 days; the weight of the seminal vesicle and of the prostate was determined on the 11th day. Of the series of compounds investigated, which included testosterone, 3 c, 17-*t*-androstanediol, androstenedione, testosterone propionate, androsterone and methyl testosterone, the last named was shown unequivocally to possess the greatest potency on administration by mouth. The authors tried to explain this fact by the presence of the methyl group in the 17-position, which is assumed to protect the adjacent hydroxyl group from fermentative processes in the digestive canal and during absorption through the intestinal wall as a result of steric hindrance.

Emmens and Parkes (8) subsequently investigated the androgenic and gynecogenic action of testosterone and methyl testosterone on capons, rats and rabbits by percutaneous, oral and parenteral administration. Testosterone was less active by mouth than by injection, in both the capon and the castrated male rat and with respect to uterus growth in castrated and immature rabbits. Methyl testosterone was, however, almost as active by mouth as by injection in causing progestational proliferation in rabbits; it had a greater activity by mouth in the other tests than testosterone (capon, castrated male rat). Methyl testosterone had a more potent androgenic action in the rat than testosterone but was less potent in capons. Methyl testosterone was always the more potent in progestational tests whichever route of administration was used. The two substances were about equally active in producing uterine growth in spayed rats and immature rabbits. On being tested for progestational activity by McPhail's method (9) methyl testosterone was found by Klein and Parkes (10) to be more potent than testosterone. These papers confirm the fact that methyl testosterone is the most potent of this class of compounds on administration by mouth.

Biskind (11) has also recently studied the question of the difference in potency between testosterone propionate and methyl testosterone on administration by mouth. He reached the conclusion that it is not due to a less pronounced decomposition of methyl testosterone by intestinal ferments but to a difference in the route of absorption; this may be, in the case of methyl testosterone, via the lymph vessels.

The activity of methyl testosterone when administered by mouth is well established from the evi-

Received for publication November 3, 1941.

dence of all of these publications. Clinical trials have also been made. Foss (12) succeeded in maintaining complete potency in a eunuch with 100 mg. daily; even 50 mg. a day proved to be effective. In cases of delayed development with genital hypoplasia, he succeeded in producing all signs of puberty, not only with regard to sexual organs but also in general physical development, with daily doses of 50 mg. for a period of 57 days. In the opinion of the author, methyl testosterone orally is capable of replacing all other methods of treatment with male hormones. Favorable results in the treatment of prostatic hypertrophy are reported by Merk (13) who obtained a satisfactory hormone action with 15 to 30 mg. a day.

More recently, Byron and Katzen (14), Kearns (15), Taper and Shelton (16) have also reported satisfactory results with methyl testosterone in eunuchism and genital hypoplasia. The external genitals increased in size, secondary sexual characteristics became more pronounced, and libido increased. Byron and Katzen observed in three eunuchs and one 10-year-old boy with genital hypofunction a gain in weight, increase in basal metabolism and a pronounced stimulant action on thoracic tissue. Comparative studies with testosterone propionate indicated that a 2½ to 3½ times larger dose of methyl testosterone is required to produce the same effect as the injected male hormone.

Simonson, Kearns and Enzer (17) studied the influence of 4 weeks of methyl testosterone treatment on working capacity and endurance in two eunuchoids and two castrates. The results show the definite increase of muscular performance and a slight increase of absolute muscular strength. McCullagh and Rossmiller (18) compared the clinical effects of methyl testosterone administered orally with those of testosterone propionate administered by injection. The 19 patients treated included cases of severe prepuberal hypogonadism, primary pituitary disease with secondary hypogonadism and functional impotence. The doses used varied from 25 to 300 mg. daily. Methyl testosterone was shown to have pronounced androgenic activity.

Dorfman and Hamilton (19) also demonstrated the androgenic activity of methyl testosterone and other substances by estimating the excretion of ketonic and nonketonic androgens in the urine after oral administration. All of the substances investigated were absorbed from the gastro-intestinal tract; methyl testosterone, although exerting a definite androgenic influence, produces only a slight increase in the concentration of androgens in the urine.

A clinical contribution to present knowledge of the favorable action of androgenic hormones in various disorders of the female genital tract has been made by Abarbanel and his coworkers (20). Following the favorable results obtained with testosterone propionate by injection, methyl testosterone tablets have more recently also been used (21). Salmon et al. (21) believe that this offers an effective form of androgenic treatment which will, after more experience has been gained, replace the others.

Spence (22) records results which allow some comparison of the various forms of treatment. Two cases of eunuchism and 4 of hypogonadism were treated with intramuscular injections of testosterone propionate, implantation of tablets of testosterone, inunction of testosterone propionate as an ointment or tincture and the oral administration of methyl testosterone. The corresponding maintenance doses required to produce about the same effect, as judged by the frequency and potency of erections, were: *a*) testosterone propionate intramuscularly, 50 to 75 mg. per week, given in two or three injections. *b*) Daily inunction of testosterone propionate as an ointment, 32 to 49 mg. per week. *c*) Daily inunction of testosterone as an ointment, 17.5 mg. per week. *d*) Oral administration of methyl testosterone, 350 mg. per week in doses of 10 mg. 5 times a day.

As is known from the literature and as our own experience has confirmed, testosterone propionate is a very active hormone with which we can successfully treat a number of genital dysfunctions in the female. Testosterone propionate, however, has two disadvantages. Firstly, there is the necessity of repeated injections and, secondly, the arrhenomimetic phenomena (change in voice, hirsutism and growth of clitoris).

In order to avoid these undesired symptoms we decided to carry out trials with sublingual therapy, in particular in women who suffered from climacteric disorders (pruritus, hot flushes and insomnia).

We were encouraged in these trials by the very good reports which had been published on the sublingual administration of desoxycorticosterone acetate. Anderson (23) found that desoxycorticosterone acetate dissolved in propylene glycol and administered by drops under the tongue is as effective as when it is given in oil subcutaneously or intramuscularly. These results were confirmed by Turnoff and Rowntree (24) who successfully treated 2 cases of Addison's disease with a solution of desoxycorticosterone acetate in propylene glycol. The patients were given 1 mg. (6 drops) under the tongue, 6 to 7 times daily, the preparation being retained for 15 minutes and then expectorated. This method did not seem to be very convenient, however, so that we decided to use especially hard-pressed tablets.

We treated in all 19 women varying in age between 27 and 67 years. Fifteen of the patients were suffering from climacteric symptoms, two from severe dysmenorrhea and two from mastodynia.

The most frequently occurring symptoms in the cases with climacteric disorders were found to be pruritus and insomnia. In the majority of cases other medicaments had been tried before methyl testosterone. In one case we observed favorable results with follicular hormone by injection, with follicular hormone ointment and with testosterone propionate by injection. In 14 of 15 cases, however, treatment with methyl testosterone was the most prolonged in effect and also the most convenient.

The dosage is, of course of decisive importance; as in hormone therapy in general, only a carefully chosen individual dosage gives satisfactory results. The method of application of the medicament might be briefly mentioned here. Thanks to the most recent knowledge on the considerably increased potency of hormones when administered sublingually, we used this method of administration in our cases. The tablets should be placed under the tongue and allowed to dissolve slowly with as little salivation as possible. The rapid and favorable effect of these tablets is explained as follows: absorption from the oral mucous membrane makes it possible to avoid the usual route through the liver, where the majority of substances undergo chemical changes and lose a large percentage of their activity; in addition the short route from the oral mucous membrane to the main vessels and the heart also favors absorption. The taste of the tablets is pleasant so that this method of application is appreciated by the patient.

The dosage given varied from one tablet of 5 mg. a day up to 30 mg. a day in severe cases. In six patients with insomnia and hot flushes, the administration of one tablet of 5 mg. every day for 2 months was sufficient. After only a few days there was slight improvement and after several weeks the symptoms had completely disappeared. These were, in general, mild cases although the usual sedatives were without effect.

Five other patients were suffering from persistent pruritus, partly with Kraurosis vulvae and leukoplakia, as a result of which there was severe insomnia. In four of these cases the complaints became less severe after treatment with 25 to 30 mg. (5–6 tablets) a day, so that the patients were able to sleep. Treatment had to be continued over a number of weeks, however, as there were otherwise cases of relapse. In one case of deficiency symptoms after roentgen-ray treatment of a uterine carcinoma, treatment with testosterone propionate in sublingual tablets was without success, but the pruritus and hot flushes were successfully treated with injections of 5 to 10 mg. of testosterone propionate 2 to 3 times a week. In the remaining 4 cases, pruritus, hot flushes and insomnia were successfully treated on an average with 2 or 3 sublingual tablets a day.

In two cases of dysmenorrhea, one of which concerned a 'neurovegetative stigmatic' with extensive genital hypoplasia, all forms of treatment including that with sublingual tablets failed. In the second case, however, the pains were somewhat alleviated by taking 30 mg. of methyl testosterone daily for 3 days before the expected menstruation and 2 days after it had started. In the 2 cases of mastodynia, the pains disappeared within a month with a dose of 15 to 30 mg. a day.

The preparation was well tolerated by all patients; no single case of nausea, or vomiting was experienced. With regard to the arrhenomimetic symptoms, such as growth of the clitoris, change in the voice and hirsutism, there occurred in one of the women a slight fluffy growth on the chin after having received 900 mg. of methyl testosterone sublingually within a month. This disappeared, however, a few days after discontinuing the treatment. In a number of patients who received large doses, smears were always taken, as experience has shown that the occurrence of the so-called atrophy cells (small epithelial cells with a large, dark-colored nucleus) is a symptom of follicular deficiency, which is the first alarm signal for overdosage and its subsequent symptoms.

In only one of the above mentioned cases were such atrophy cells present; in this case treatment was discontinued without further trouble for the patient.

The number of cases treated is much too small for far-reaching conclusions to be made. It is, however, seen that methyl testosterone as sublingual tablets constitutes an effective and convenient form of treatment of climacteric deficiency symptoms. We are justified even today in stating that tablets for sublingual dosage are well tolerated, comparatively harmless and have a prolonged action. By taking vaginal smears regularly twice a month characteristic alterations are recognized at an early stage and the disagreeable and undesirable effects of methyl testosterone can be avoided.

SUMMARY

A short review of the literature on experimental and clinical observations with methyl testosterone in males and females is given. A report is made on 19 cases (15 of climacteric disorders, 2 of dysmenorrhea and 2 of mastodynia) treated with methyl testosterone in sublingual tablets.

In moderately severe cases of climacteric disorders 2 to 3 tablets of 5 mg. each a day were sufficient; in more severe cases 25 to 30 mg. (5–6 tablets). In one case in which 900 mg. of methyl testosterone was given in one month, a slight growth of hair was produced in the chin; the hair disappeared within a few days after discontinuing treatment. Special atten-

tion is drawn to control of the dosage by means of vaginal smears in order to avoid any possible arrhenomimetic symptoms.

Although the number of cases is small, the particularly favorable and convenient method of administration of methyl testosterone as sublingual tablets is illustrated, although this communication is meant to serve only as a stimulation to further investigation of this compound and its method of application.

We wish to express our appreciation to the Society of Chemical Industry in Basle (Ciba) for supplying us with methyl testosterone sublingual tablets.

REFERENCES

1. Ruzicka, L. M. W. Goldberg and H. R. Rosenberg: *Helvetica Chimica Acta* 18: 1487. 1935.
2. Ruzicka, L., and H. R. Rosenberg: *Helvetica Chimica Acta* 19: 357. 1936.
3. Deansley, R., and A. S. Parkes: *Biochem. J.* 30: 291. 1936.
4. Shapiro, H. A.: *Chem. & Ind.* 55: 1031. 1936.
5. Shapiro, H. A.: *J. Endocrinol.* 1: 1. 1939.
6. Deanesly, R.: *J. Endocrinol.* 1: 300. 1939.
7. Miescher, K., and E. Tschopp: *Schweiz med. Wchnschr.* 68: 1258. 1938.
8. Emmens, C. W., and A. S. Parkes: *J. Enodcrinol.* 1: 323. 1939.
9. McPhail, M. K.: *J. Physiol.* 83: 145. 1934.
10. Klein, M., and A. S. Parkes: *Proc. Roy. Soc. London, s. B.* 121: 574. 1937.
11. Biskind, G. R.: *Proc. Soc. Exper. Biol. & Med.* 43: 259. 1940.
12. Foss, G. L.: *Brit. M. J.* 2: 11. 1939.
13. Merk, K.: *Ztschr. f. Urol.* 33: 573. 1939.
14. Byron, C. S., and P. Katzen: *J. Clinical Endocrinology* 1: 359. 1941.
15. Kearns, W. M.: *J. Clinical Endocrinology* 1: 126. 1941.
16. Tager, B. N., and E. K. Shelton: *J. Clinical Endocrinology* 1: 131. 1941.
17. Simonson, E., W. A. Kearns and N. Enzer: *Endocrinology* 28: 506. 1941.
18. McCullagh, E. P., and H. R. Rossmiller: *J.A.M.A.* 116: 2530. 1941.
19. Dorfman, R. J., and J. B. Hamilton: *J. Biol. Chem.* 133: 753. 1940.
20. Abarbanel, A. R., H. M. Radman and D. Silberman: *Am. J. Obst. & Gynec.* 39: 332. 1940.
21. Salmon, U. J., S. H. Geist, J. A. Gaines and R. I. Walter: *Am. J. Obst. & Gynec.* 41: 991. 1941.
22. Spence, A. W.: *Quart. J. Med.* 36: 309. 1940.
23. Anderson, E., W. Haymaker and E. Henderson: *J.A.M.A.* 115: 2167. 1940.
24. Turnoff, D., and L. G. Rowntree: *J. A. M. A.* 116: 206. 1941.

Subjective Symptoms and Therapeutic Response in the Control of Estrogen-Progesterone Therapy in Menstrual and Reproductive Disorders

PHILIP F. SCHNEIDER, M.D.

From the Department of Obstetrics and Gynecology, Evanston Hospital, Evanston, Illinois

IT HAS LONG BEEN OBVIOUS that the two ovarian hormones estrogen and progesterone have a definite relationship to each other and to menstrual and reproductive function. An antagonistic relationship between estrogen and progesterone was first suggested by Smith and Smith in 1931 (1). Prior to the presentation of a gravimetric method for the estimation of urinary pregnandiol by Venning (2) in 1937, endometrial biopsy was the only means available for the estimation of progesterone activity. Wilson, Randall and Osterberg (3) have presented evidence indicating that endometrial changes do not provide an accurate index to the variations of urinary pregnandiol levels. This observation would seem to indicate that endometrial changes are of qualitative rather than quantitative significance. Lack of quantitative means for the determination of progesterone activity has undoubtedly been responsible for the paucity of considerations of estrogen and progesterone relationship in the literature. Theories for estrogen and progesterone therapy have been based primarily on conclusions derived from the results of animal or human experimentation. In such experimentation the subject has invariably been either a normally functioning endocrine mechanism or a castrate. The favorable results obtained by the application of these theories in the treatment of menopausal disorders have not been duplicated when theories derived from experimental evidence in normal animals have been applied in the treatment of disorders resulting from abnormal endocrine function encountered prior to the menopause. In spite of the fact that some encouraging results have been reported in the treatment of threatened abortion, habitual abortion, dysmenorrhea, menorrhagia and metrorrhagia with progesterone, and in nausea and vomiting of pregnancy and certain other premenopausal disorders with estrogens, the results have not been comparable to those obtained in menopausal disorders. Consideration of the results in the present series of cases suggests the possibility that the attempt to apply such theories in ovarian imbalances prior to the menopause may be an important factor in the failure to obtain more consistent results with estrin and progesterone therapy.

In the present series of 578 cases, the observation (4) that menstrual and reproductive disorders due to estrogen and progesterone imbalances were always accompanied by many of the same subjective symptoms encountered in the menopausal deficiencies was utilized. The presence of such symptoms was accepted as evidence of estrogen-progesterone imbalance, while response to therapy in the form of relief or exaggeration of these symptoms served as evidence of the type of deficiency which existed.

Because of the importance of meticulous consideration of detail, the syndrome previously described (5, 6) is again presented.

Syndrome suggestive of estrogen-progesterone (5) imbalance prior to the menopause. *a*) exhaustion; *b*) nervousness and irritability; *c*) depression; *d*) emotional instability; *e*) breast tenderness; *f*) cramping or bearing down; *g*) neckache; *h*) legache; *i*) headache with or without nausea; *j*) backache; *k*) insomnia; *l*) dizziness; *m*) hot flushes; *n*) vaginal irritation; *o*) frigidity; *p*) psychotic disturbances such as apprehension of social contacts, disturbing dreams, and suicidal or homicidal tendencies.

Associated conditions. *a*) hypertension; *b*) atrophic rhinitis; *c*) irritable colon; *d*) arthralgias; *e*) skin eruptions; *f*) migraine (menstrual or menopausal); *g*) pelvic pain in the absence of pathologic findings.

In the present series of cases all patients in whom any combination of symptoms of the above syndrome was encountered in association with disturbance of menstrual function were placed on estrogenic therapy. Relief of subjective symptoms with improvement or

Received for publication August 22, 1941.

relief of the accompanying disturbances occurred in a large percentage of these patients. The method of diagnosis and determination of dosage has been previously described (6), and only the essentials are again presented. These essentials are based on the observation that the exact amount of estrogenic substance[1] when administered parenterally will relieve subjective symptoms within 45 minutes for a period of 6 or 8 hours or longer. These amounts rarely exceed 300 I.U., and dosage in each individual is begun with 100 I.U. and continued in daily injections.

In a small but rather definite group, however, it was not only impossible to obtain relief but also both subjective symptoms and abnormal menstrual conditions appeared to be definitely exaggerated or intensified. Cessation of estrogenic therapy was consistently followed by prompt decrease in exaggeration of the condition. In most of the cases in this smaller group the administration of progesterone produced clinical results comparable to those obtained by estrogenic therapy in the larger group. The consistency with which these results were obtained when applied in menstrual disorders, and in sterility, habitual abortion, and nausea and vomiting of pregnancy, indicated that the syndrome originally described (4) as suggestive of estrogenic deficiency, might when encountered prior to the menopause, be due to either estrogen or progesterone deficiency, and led to the hypothesis that menstrual and reproductive function might be dependent on balance between estrogen and progesterone.

TABLE 1

	No. Cases	Successes		Failures[1]	Incomplete
		Estrogens	Progesterone		
Group A					
Menopausal disorders	107	103	0	3	1
Amenorrheas, oligomenorrhea, hypomenorrhea	96	77	3	10	6
Totals for *Group A*	203	180	3	13	7
Group B					
Premenopausal[2]	38	27	2	6	3
Dysmenorrhea	71	54	12	4	1
Menorrhagia	113	61	36	14	2
Metrorrhagia	10	5	2	3	0
Sterility	57	16	7	24	10
Habitual abortion	16	9	7	0	0
Threatened abortion	24	7	5	11	1
Nausea or nausea and vomiting	46	28	17	0	1
Totals for *Group B*	375	207	88	62	18
Total cases	578	387	91	75	25

[1] Partially successful results were classified as failures.
[2] Women of menopausal age who presented only subjective symptoms and no complaints permitting classification under other categories.

The essentials of therapeutic response (6). It has been observed that three types of reaction occur following parenteral administration of estrogenic substances. These reactions occur within one hour after administration and though transitory are of considerable significance. These reactions are *a*), total absence of effect which usually indicates that estrogenic deficiency exists and that the initial dose has been inadequate and should be increased; *b*) an improvement or relief of symptoms, or a feeling of wellbeing for a period of 6 to 8 hours which is evidence that an actual estrogenic deficiency exists and therapy should be continued; *c*), an exaggeration of the symptoms, extreme exhaustion, pelvic pain, or bearing down sensation; if transitory and followed by relief of the original symptoms, indicates that estrogenic deficiency exists but that dosage was excessive and should be decreased; if prolonged and *not* followed by relief of original symptoms, that estrogenic deficiency does not exist and that progesterone therapy is indicated.

TABLE 2

	No. Cases	Successes		Failures	Incomplete
		Estrogens	Progesterone		
Dysmenorrhea	71	54	12	4	1
Menorrhagia	113	61	36	14	2
Metrorrhagia	10	5	2	3	0
	194	120	50	21	3

In the present series, for the purpose of classification, only the most obvious disturbance or complaint was utilized when several conditions existed simultaneously.

Table 1 demonstrates the presence of two distinct therapeutic types which have been separated into *groups A* and *B*. It will be noted that in *group A*, consisting entirely of various forms of amenorrheic disorders, successful results were obtained in almost 90 per cent of the cases with the estrogens. In *group B*, composed of various forms of menstrual and reproductive disturbances successful results were obtained in over 50 per cent of the cases by means of the estrogens, while less than 25 per cent of the total number responded in a like manner to progesterone therapy. These results would seem to be logical in view of the rather well established fact that absence of ovulation in amenorrheic conditions results in absence of progesterone activity, while in the pres-

[1] The estrogen (Amniotin in oil) was supplied by E. R. Squibb and Sons, New York City.

ence of ovulation or placentation in other menstrual and reproductive disorders progesterone activity is always a factor which must be considered.

Further analysis of *group B* reveals that of the 38 cases classified as premenopausal the predominant deficiency was estrogenic, only 2 patients responding to progesterone.

The results in dysmenorrhea, menorrhagia, and metrorrhagia, as demonstrated in table 2, indicate estrogenic deficiency as a more frequent etiologic factor than progesterone deficiency. In each of these conditions, contrary to expectations based on our concept of progesterone activity, a far greater number responded to estrogenic therapy than to progesterone, 120 being relieved by the estrogens as compared to 50 responding to progesterone.

TABLE 3

	No. Cases	Successes		Failures	Incomplete
		Estrogens	Progesterone		
Habitual abortion	16	9	7	0	0
Threatened abortion	24	7	5	11	1
Totals	40	16	12	11	1

The results in threatened and habitual abortion in table 3, although the number of cases is too small to permit conclusive deductions, are of interest and possible importance. In 16 cases of habitual abortion (previous losses of 2 or more pregnancies) all were carried to successful termination with a living child in each instance. In 9 cases this was accomplished with estrogenic therapy, and in 7 with progesterone. In every instance therapy was instituted either prior to conception or early in pregnancy prior to any threat to abort. In contrast in the 24 cases of threatened abortion where therapy was not instituted until after manifestations such as bleeding and cramping had occurred, it was possible to preserve the pregnancy in only 12 or 50 per cent of the cases. Here again the proponderance of estrogenic deficiency as an etiologic factor is indicated, with 7 cases responding to the estrogens and 5 cases to progesterone.

The series of 57 cases of sterility listed in table 1 included only those in which tubal occlusion and male sterility had been eliminated. The fact that pregnancy occurred in 23 cases following therapy would indicate estrogen and progesterone imbalance as an etiologic factor of considerable importance.

CONCLUSIONS

In the present series of cases, subjective symptoms and therapeutic response have been used, both as a diagnostic measure to determine the type of deficiency and as criteria for dosage.

Relief of subjective symptoms was accompanied by correction of the conditions presented by the patient in an impressive percentage of the cases treated.

The results would seem to suggest that *a*), menstrual and reproductive function may be dependent on balance between estrogen and progesterone; *b*) that estrogen and progesterone deficiencies may be relative rather than quantitative; *c*) that subjective symptoms and therapeutic response may be utilized as therapeutic guides until more accurate methods become available, and *d*) that failure to obtain consistent results in many of these conditions may have been due to excessive therapy.

The hormone preparations were supplied by Ayerst, McKenna & Harrison, Ltd., Rouses Point, N.Y., E. R. Squibb & Sons, New York City and The Schering Corporation, Bloomfield, N. J.

REFERENCES

1. SMITH, G. V., AND O. W. SMITH,: *J. A. M. A., Tr. Sect. Obst., Gynec. & Abd. Surg., A. M. A.* 189. 1931.
2. VENNING, E. H.: *J. Biol. Chem.* 119: 473. 1937.
3. WILSON, R. B., L. M. RANDALL, AND A. E. OSTERBERG,: *Am. J. Obst. & Gynec.* 37: 59. 1939.
4. SCHNEIDER, P. F.: A syndrome suggestive of estrogenic deficiency. *Am. J. Obst. & Gynec.* 31: 782. 1936.
5. SCHNEIDER, P. F.: Estrogenic therapy of menopausal disorders. *Illinois M. J.* 1939.
6. SCHNEIDER, P. F.: The value of endocrines in adult female life. The Medical Press and Circular, Vol. CC1, No. 5204. London, 1939.

Weekly Urinary Pregnandiol Determinations throughout the Last Seven Months of Pregnancy in Two Cases of Primary Sterility

PHILIP F. SCHNEIDER, M.D.
From the Department of Obstetrics and Gynecology, Evanston Hospital, Evanston, Illinois

TWO CASES OF PRIMARY STERILITY 7 and 4 years in duration respectively, are presented. By means of the Rubin and Hühner tests, tubal occlusion and male sterility had been excluded. Daily vaginal smears over a period of several months in 1938 suggested estrin deficiency in one patient and progesterone deficiency in the other. By utilizing subjective symptoms, therapeutic response, and the vaginal smear (1–4), adequate dosage was determined in each instance and the patients placed on the therapy indicated. Pregnancy occurred almost simultaneously in both patients within three months, and in each instance was accompanied by nausea and vomiting at 6 to 8 weeks, and by threat to abort manifested by bleeding and cramping. These disturbances were relieved by continuation and regulation of estrogenic therapy in one patient, and progesterone in the other. In the patient presenting estrogenic deficiency, therapy was continued until the fourth month, while in the patient having a progesterone deficiency, therapy was continued until the seventh month. Weekly urinary pregnandiol determinations were obtained in each case during the last 7 months of pregnancy.

CASE HISTORIES

Case 1. The patient, 28 years of age, was first seen on December 14th, 1937, with a primary sterility of 7 years' duration. The menses began at 11 years of age, were of the regular 28-day type, lasting 3 to 4 days, and were moderate to scant in amount, with no pain. Prodromal symptoms consisted of breast tenderness, nervousness, irritability, depression, and exhaustion, and were variably present for 1 or 2 days prior to the menses. Tubal patency was confirmed on Jan. 4th, 1938, by the Rubin method, the gas passing easily at 70 to 80 mm. of Hg. The Hühner test revealed normal spermatazoa in the husband. Vaginal smears suggested estrogenic deficiency and therapy was instituted in February 1938. Breast tenderness, cramping, and depression were definitely relieved by estrogens.[1] The last menstrual period occurred April 21st, 1938, and the pregnancy test was negative on May 25th, 1938, but positive when repeated on June 3rd, 1938. Nausea and vomiting began on May 24th, 1938, and at the same time threat to abort with cramping and bleeding occurred, both conditions being relieved by increasing the daily dose of estrogen. All medication was discontinued on Aug. 10th, 1938, and pregnancy progressed uneventfully to term on Jan. 28th, 1939, with spontaneous delivery of a normal female child weighing 7 lb. 3 oz.

Case 2. The patient, 26 years of age, with a primary sterility of 4 years' duration, was first seen on Nov. 30th, 1936. There was a history of appendectomy and oöphorectomy within the first year of marriage. Previous tubal inflation and Hühner tests by competent obstetricians, repeated twice within three years, were accepted as evidence establishing tubal patency in the patient, and the presence of normal spermatazoa in the husband. The menses which had started at 12 years of age were irregular at 26 to 31 day intervals, lasting 8 days, and excessive with no pain or history of prodromal symptoms. Examination revealed a small infantile uterus to the right of the midline, the right ovary could not be palpated, and the left ovary was slightly enlarged. Endocrine therapy was administered from Jan. 21st, 1937, to Aug. 2nd, 1937, with the result that when estrogenic therapy produced extreme vaginal irritation, and subsequent progesterone therapy caused cramping, medication was discontinued as unsatisfactory. Pregnancy occurred 4 months after cessation of therapy but was followed by abortion in spite of the administration of progesterone. The last menstrual period had occurred on Dec. 23rd, 1937, cramping and bleeding beginning on Feb. 9th, 1938. Pregnancy test was positive on Feb. 10th, 1938, and abortion occurred on Feb. 24th.

On the assumption that the previous endocrine therapy must have been responsible for the pregnancy, daily vagi-

Received for publication August 18, 1941.

[1] The estrogens (Amniotin and Emmenin) were supplied by E. R. Squibb and Sons, New York City and by Ayerst, McKenna and Harrison, L'td., Rouses Point, N. Y., respectively.

nal smears were taken from April 23rd to June 2nd, 1938. These smears indicated a progesterone deficiency. The patient reported extreme exhaustion on May 31st, 1938, and progesterone[2] relieved the exhaustion within one hour. Progesterone, 1/10 RB.U. was administered on June 2nd, and 4th, July 5th, and 7th; 1/5th unit on July 11th, 14th,

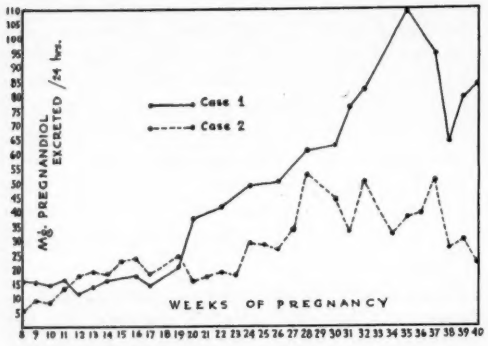

Fig. 1. WEEKLY PREGNANDIOL EXCRETION VALUES in *cases 1* and *2*.

16th, 19th, 25th, Aug. 1st, and 4th, 1938. The last menstrual period occurred on June 15th, 1938. Pregnancy test became positive on July 28th, 1938, nausea and vomiting, headache, exhaustion, and backache and cramping, accompanied by slight bleeding occurred on Aug. 8th, and were controlled from Aug. 8th to Jan. 12th, 1939, with 21 injections of progesterone ranging from 1/4th to 1/10th RB.U. doses. No additional therapy was necessary thereafter and the pregnancy terminated normally with the delivery of a 6 lb. female child on March 24th, 1939.

DISCUSSION

Weekly determinations of urinary pregnandiol were obtained throughout pregnancy beginning at the eighth week in both instances. The method described by Venning (5) was utilized and all determinations were carried out on the urinary excretion for 24-hour periods. Therapy was continued in *case 2* until the 30th week of the pregnancy and until *week 16* in *case 1*. In both patients complete abeyance of symptoms was obtained and the usual discomforts encountered during pregnancy were notably lacking. In figure 1, the pregnandiol determinations of *case 1* are represented by the solid line, those of *case 2* by the broken line, the vertical plane representing the milligrams of pregnandiol, and the horizontal representing the weeks of pregnancy. It is of interest to note that the two curves are almost analogous to the highest and lowest levels presented as normal limits during pregnancy by Venning and Browne (6), and also correspnd to the high and low values as indicated by Wilson, Randall and Osterberg (7). *Case 1* in which the evidence would indicate a relative deficiency of the estrogens and an excess of progesterone provided the maximum curve, while in *case 2*, in which the evidence suggested an excess of the estrogens with a deficiency of progesterone, the minimal pregnandiol values occurred. These values in *case 1* ranged from 16.95 mg. at *week 8* to a maximum of 109 mg. at *week 31*, decreasing thereafter only to 64.27, 79.75, and 83.69 mg. at *weeks 38*, 39, and 40 respectively. In *case 2* the pregnandiol levels ranged from 5.97 mg. during *week 8* to a high of 52.45 mg. at *week 27*, and with a decrease to 26.35, 30.02, and 22.85 mg. at *weeks 38*, 39, and 40 respectively.

The difference in the levels of pregnandiol excretion and the normal course of the prenatal period and labor in these two cases after correction of estrogen and progesterone imabalance would seem to indicate that while therapy seems to have been of clinical value in overcoming sterility, nausea and vomiting, and threatened abortion, there is no evidence which indicates that therapy in either case influenced the pregnandiol levels. Despite the fact that low pregnandiol levels were encountered in the patient where progesterone therapy was of clinical value, and abnormally high pregnandiol levels were obtained in the case where estrin therapy produced clinical results, there is no evidence that therapy in either instance produced a demonstrable change in the pregnandiol values. If correct, this observation would tend to corroborate the suggestion by Novak (8) that balance between estrogen and progesterone, rather than quantitative values is the important factor. The extremely small dosages used in comparison with the present tendency toward massive dosages are considered by the author as a significant factor in the results obtained.

The author desires to express his appreciation to Doctor G. E. Wakerlin, chief of Department of Physiology, University of Illinois School of Medicine, for his cooperation in obtaining the urinary pregnandiol determinations which served as the basis for this study.

REFERENCES

1. SCHNEIDER, P. F.: A syndrome suggestive of estrogenic deficiency. *Am. J. Obst. & Gynec.* 31: 782. 1936.
2. SCHNEIDER, P. F.: Estrogenic therapy of menopausal disorders. *Illinois M. J.* 1939.
3. SCHNEIDER, P. F.: Prophylactic endocrine therapy in artificial menopause. *Am. J. Obst. & Gynec.* 37: 861. 1939.
4. SCHNEIDER, P. F.: Subjective symptoms and therapeutic response in the control of estrogen-progesterone therapy in menstrual and reproductive disorders. *J. Clinical Endocrinology* 2: 120. 1942.
5. VENNING, E. H.: *J. Biol. Chem.* 119: 473. 1937.
6. BROWNE, J. S. L., AND E. H. VENNING: *J. Clin. Investigation* 16: 678. 1937.
7. WILSON, R. B., L. M. RANDALL, AND A. E. OSTERBERG: *Am. J. Obst. & Gynec.* 37: 59. 1939.
8. NOVAK, E.: Clinical Employment of the Female Sex Hormones. *Endocrinology* 25: 423. 1939.

[2] The progesterone (Proluton) was supplied by the Schering Corporation, Bloomfield, New Jersey.

Adrenal Tumor in Female Infant

With Hypertrichosis, Hypertension, Overdevelopment of External Genitalia, Obesity, but Absence of Breast Enlargement

[Pseudo-Sexual Precocity]

FRANK C. NEFF, M.D.
GALEN TICE, M.D.
GEORGE A. WALKER, M.D., AND
NELSE OCKERBLAD, M.D.
From the Departments of Pediatrics, Roentgenology, Surgery, and Pathology, School of Medicine, University of Kansas, Kansas City, Kansas

THE SEX AND AGE of the individual have an influence upon the character of the symptoms and functional disturbances produced by tumors of the adrenal gland whether these are benign or malignant; for instance, the term 'Cushing's syndrome' does not cover the various types which have recently become known. Case reports confirm the occurrence of certain common characteristics, but as in most diseases, an analysis of the symptomatology may show variations. Sexual precocity in the young boy, enlarged mammary glands in the adolescent male and masculinization of the preadolescent female, are examples of such clinical endocrine abnormalities.

The case reported here is that of an infant, with a syndrome which is especially characteristic in a young female child who has an adrenal cortical tumor. Lisser(1) has termed this "pseudo-sexual precocity" to distinguish it from "true sexual precocity" caused by tumors of the ovary of the granulosa cell type.

CASE REPORT

Baby Girl X was born July 8, 1939, weighing 7¾ pounds; height, 21 inches. She gained steadily and at 7 months the weight was 18 pounds, the height 28.5 inches. At 8 months changes in appearance began with an unusual growth of body hair; at 11 months acne appeared and continued on the face and chest. The teeth and weight were normal at one year of age.

Findings at sixteen months. On Oct. 29, 1940, the patient was admitted to the hospital. There was a tendency to obesity; she was able to stand but was not walking much. There was a generalized hirsuties, heaviest over the back, shoulders, axillae, and genitalia. The labiae were hypertrophied, and of adult appearance.

The blood pressure varied from 140 to 180 mm. Hg systolic. The red blood cell count was 6,830,000 and the hemoglobin 76 per cent. The blood chemistry findings were normal, including sugar and glucose tolerance. The non-protein nitrogen was 34.5 mg. per cent; the sodium chloride 460 mg. per cent.

Roentgenogram. The spine, pelvis and hips were normal in form but the bones were massive and the ossification centers were advanced to 2 years or more. The skull was large; the sella turcica was small. By aid of a retrograde pyelogram, a mass was seen surmounting the upper pole of the left kidney. A stereogram indicated a mass adjacent to the posterior rather than to the anterior portion of the upper pole.

Cystoscopic examination. Seven cc. of urine was collected at once from the left ureteral catheter which was indicative of a pathological state on that side.

Fig. 1. APPEARANCE OF INFANT ON ADMISSION TO HOSPITAL AT AGE OF 16 MONTHS.

Received for publication October 16, 1941.
Read in part at the Fifty-third annual session of the American Pediatric Society, Hot Springs, Virginia, May, 1941, with the presentation of a colored movie film.

Air injection. A tumor mass was outlined by a small amount of air introduced into the perirenal space.

Operation was delayed nearly one month because of an intercurrent upper respiratory infection. During the weeks that elapsed after the foregoing diagnostic measures were made, the tumor became palpable.

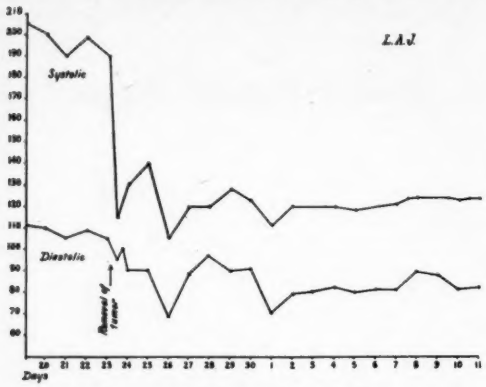

Fig. 2. Chart of blood pressures recorded before and after operation for adrenal tumor.

Preoperative findings. The blood pressure was 200 mm. Hg systolic, 110 diastolic. A few days were allowed for preparation (2) of the patient consisting of a potassium-free diet and sodium chloride and citrate given liberally.

Operation, Nov. 23, 1940. The patient was placed on the table with her right side downward. Two large adhesive strips were used to fasten her securely to the table. The table was then broken so that the greatest amount of space could be obtained in the loin. A curved lumbar incision was made exposing the perirenal space. The kidney was picked up and the fatty envelop opened. When the kidney was pushed down, the tumor presented itself as a rounded mass in the area of the dome of the diaphragm. This was quickly dissected free and pulled downward. The vein going into this tumor presented toward the operator. This vein was grasped with a clamp in order to prevent the hormone going into the blood stream. The pedicle to this tumor was then clamped and tied, and the tumor freed and cut away. During the operation the blood pressure rose to 180 and then to 200 mm.Hg. It fell as soon as this vein was clamped, but it did not go lower than 80 mm.Hg systolic. The patient was taken from the operating room in good condition. Immediately afterward th white cell count was found to be 44,850 with 84 per cent polymorphonuclear leucocytes. The count gradually fell to a normal level.

The blood chemistry, including non-protein nitrogen, creatinine, and sugar were within normal limits on Nov. 22, 25, and Dec. 4. The sodium chloride was 301.7 mg. on Nov. 23; 326.7 mg. on Nov. 25; and 329.6 mg. on Dec. 6.

Treatment. Adrenal cortical hormone and fluids by clysis were used during and following the operation. Sedation was with paregoric. The infant was dismissed as well on Dec. 11, 1940.

Characteristics of the tumor. The tumor weighed 96 grams; it was spherical in shape and 6 cm. in diameter. There was a thin capsule; a portion of adrenal cortical tissue 10×2×2 mm. could be identified on the surface.

Histologically the growth consisted of small groups of round, oval, or polyhedral cells with abundant c toplasm; they were separated by delicate septa of cor

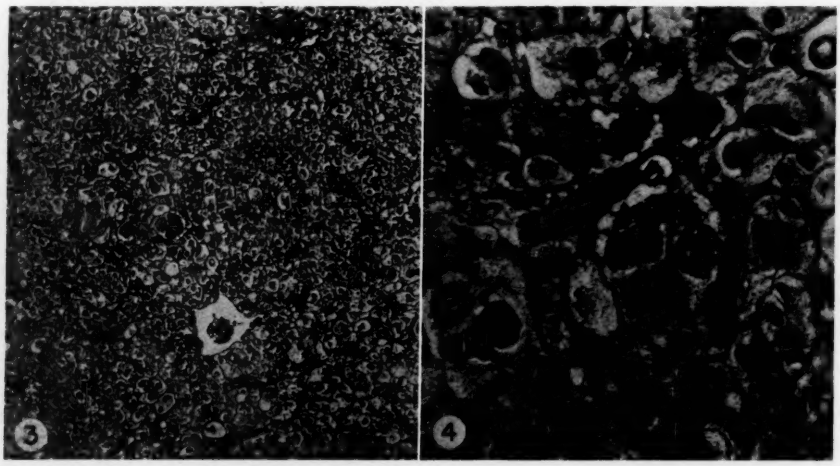

Fig. 3. Photograph of tumor section. This shows the solid cellular structure, without definite septa or any tendency to alveolar formation. Note the intimate relation of the tumor cells to the endothelium of the capillaries. × 100.

Fig. 4. Photograph of tumor section. This shows the marked variation in size and shape of the cells, variable staining reaction of the nuclei, hyperchromatism and several multinucleated giant cells of neoplastic type. Note the pale staining areas in the cytoplasm of many cells. These areas proved to be lipoid material. × 460.

nective tissue (fig. 3 and 4). Numerous giant cells with single or multiple nuclei were present. There was considerable variation in the structure of the nuclei, many being large, irregularly lobulated and hyperchromatic; mitotic figures were frequently seen. Many cells showed vacuolization of the cytoplasm and gave positive reactions with fat stains. Brown granules were seen in many of the cells when the tissue was treated with chrome salts; silver impregnation permitted a diagnosis of chromaffinoma or pheochromocytoma.

Degree of recovery following removal of the tumor. Within 3 months most of the hirsutism had disappeared; the acne was less noticeable. The child's activity level became normal and there was a loss of some of the abundant fat which had been noticeable about the cheeks and the middle of the body. Six months after the operation the labiae and the pubic hair were less prominent. The axillary and dorsal hair had entirely disappeared.

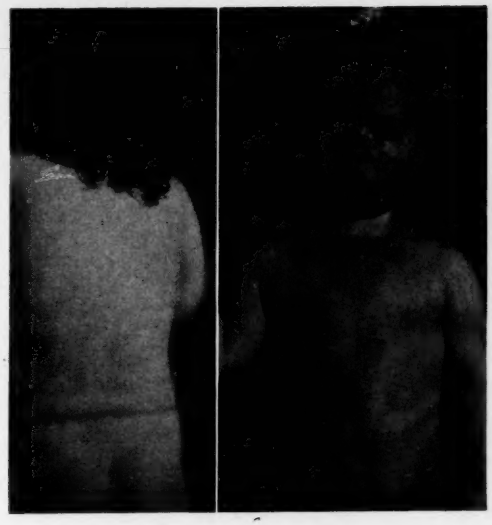

Fig. 5. Appearance of child at 2 years of age, 9 months after operation for removal of adrenal tumor

DISCUSSION

It is difficult to correlate the structure of this tumor with the disturbances in physiology and changes in appearance of the child. It is known that there are one or more hormones produced in the adrenal cortex which play a part in the normal sexual development. In most of the examples of adrenal tumor associated with disturbances in development of sexual characteristics there has been a tumor of the cortex and usually a precocious development of male characteristics. However, there are reports of cases in which a tumor of the adrenal cortex has been associated with feminization, gynecomastia, atrophy of penis and testes, loss of libido, and usually with obesity. Hence it appears that adrenal cortical tumors may cause a disturbance of sexual development in either direction. The tumor presented here is a medullary tumor and would not be expected to cause any sexual changes. Ordinarily a medullary tumor is associated with paroxysmal hypertension, which was present in this case. One can only suggest that this tumor interfered with the function of the cortical tissue through mechanical effects. The portions of adrenal cortex stretched over the surface of the tumor were distinctly separated from it by a capsule. This cortical tissue was not atrophic and presumably it was producing an increased amount or a perverted type of secretion which may be held responsible for the changes noted clinically.

The fact is recognized that the two parts of the adrenal gland produce tumors that are entirely different pathologically. The two better known varieties of tumor developing in the medulla are the neuroblastoma and the ganglioneuroma; but the third variety, the paraganglioma, affects chromaffin cells not only in the medulla but in other regions of the body. The paraganglioma seems to be found in advanced life usually and may occur in either sex. A chromaffin tumor of the extramedullary type is said to produce the characteristic epinephrine.

In this case, the medullary tumor grossly seemed to be distinct from any connection with the cortex, because of a thick capsule. Eisenburg and Wallerstein, (3) in discussing paraganglioma, state that in most of these tumors, especially the large ones, the entire gland is involved in a tumor mass which obliterates the medulla but retains a thin rim of cortex.

The relationship between the pituitary gland and the adrenal cortex has recently been reviewed by Swann (4). He has found that control by the pituitary varies from maximal to minimal and is complete with respect to fat, protein, and sugar metabolism; control by the pituitary is possible but not proven in experimental hypertension.

An involvement of the adrenal by tumor makes it necessary to have a reservation as to what the growth will finally prove to be. Whether this tumor is benign will require prolonged observation of the patient, since carcinoma or a mixed tumor of the adrenal, with metastasis, is the most common final diagnosis.

REFERENCES

1. Reilly, W. A., H. Lisser and F. Hinman: Adrenal cortical syndrome in preadolescent girls. *Endocrinology* 24: 91. 1939.
2. Walters, W., and E. J. Keplar: Adrenal cortical tumors and their treatment. *Ann. of Surg.* 107: 881. 1938.
3. Eisenberg, A. A., and H. Wallerstein: Pheochromocytoma of suprarenal medulla (paraganglioma). *Arch. Path.* 14: 6. 1932.
4. Swann, H. G.: The pituitary-adrenocortical relationship. *Physiol. Rev.* 20: 493. 1940.

Pituitary Antagonists in the Treatment of Bronchial Asthma

[Estrogenic Therapy in Asthma]

EDMUND E. BEARD, M.D.
AND WILLIAM P. GARVER, M.D.
Cleveland, Ohio

CLINICAL OBSERVATIONS of the marked influence of the emotions upon allergic diseases, such as asthma and urticaria, and experimental evidence pointing directly to modification of the localization and severity of atopic reaction through the autonomic nervous system, have led to general acceptance of the importance of the autonomic nervous system as a factor in the mechanism of such reaction (1). Modern therapy of diseases in this group makes use of agents affecting the nervous system. General sedatives, calcium and the parathyroid hormone, atropin, aminophyllin and epinephrin are of this nature. Of these epinephrin is the most effective, but the short duration of its action, the failure of its chronic administration to bring about sustained improvement, and especially the development of so-called 'adrenalin resistance,' indicate that it has no power to modify fundamentally any nervous system disturbance which might be responsible for the appearance of the allergic reaction.

Since the autonomic nervous system and the endocrine glands are closely associated both anatomically and functionally it would appear that hormonal balance could have some bearing upon susceptibility to atopic response. Evidence for the validity of this concept is furnished by the common observation that allergic states are prone to change markedly at puberty, during the various phases of the menstrual cycle, pregnancy, and the climacteric. That such changes are not consistent, being in one individual in the direction of improvement and in another for the worse, may argue against direct hormonal effect, but does not argue against some mediate hormonal effect, such, for example, as disturbance of autonomic balance.

The following report is of a case of Dr. R. B. Poling of Youngstown, Ohio. We have had the opportunity to follow the progress of the patient over a period of four and one-half years of illness. During the last twenty-four months of this period she had allergic vasomotor rhinitis and bronchial asthma. This patient has furnished an opportunity for observations bearing on the nature of the endocrine-autonomic-allergic mechanism. Her repeated response to sex hormone therapy is the most important of these observations.

Received for publication April 28, 1941, and later extended to include subsequent data.

CASE REPORT

A white female, married, mother of 5 children, had never had allergic manifestations. A paternal aunt, a sister, and the son of a brother had had severe bronchial asthma most of their lives. A niece had had vasomotor rhinitis appearing coincidentally with neuro-vascular menopausal disturbance, both apparently having been benefited by estrogen administration. Another niece and another nephew are now suffering from asthma.

The patient had a large nodular thyroid which had remained unchanged for at least forty years. She had gone through an uneventful climacteric, the menses ceasing in the late forties, with no evidence of thyroid disturbance.

In January 1937 at the age of 75 years she had the first serious illness of her life. This was a generalized fibromyositis which gave rise to a low grade fever, constant pain, sleeplessness and a weight loss of 50 pounds. With the use of sulfanilamide and the removal of two infected teeth this condition subsided at the end of six months. In October 1937 manifest hyperthyroidism developed. In December, 1937 a sub-total thyroidectomy was performed.[1] Convalescence was satisfactory and relief of the symptoms of hyperthyroidism seemed complete.

In May 1939 there developed what the patient considered to be a peculiar head cold with a profuse nasal discharge. In the next month she became somewhat short of breath on exertion, and in early July began to have paroxysms of coughing. The diagnosis of bronchial asthma was made, and she was treated by the usual routine including epinephrin. Beginning at this time and re-appearing each time her asthma became worse, were sudden sweats which at times were drenching. These came without apparent immediate cause, and were dismissed as being an expression of her weakness, probably contributed to by increased respiratory effort and confinement to bed. At first she responded readily to epinephrin, but by the end of July she was in status asthmaticus and was taken to the hospital and kept in an oxygen tent for two weeks. Skin

[1] The subtotal thyroidectomy was performed by Dr. Carl Lenhart.

tests, direct and by passive transfer, were done and sensitivity to house dust was discovered. The blood eosinophile count was 11%. Dust extract injections were begun and continued until a month before death. On Aug. 14, 1939, while still using as many as 7 injections of one-fourth cc., each of epinephrin per 24 hours, the patient returned home to an 'allergen-free' room with linoleum-floor, no hangings, pollen air-filter in the window, and allergen-proof casings. Epinephrin spray, epinephrin in oil, elimination diets, aminophyllin and histaminase[2] were tried without apparent advantage over the previous therapeutic regime. From Sept. 1, 1939 she became progressively worse and was returned to the hospital Sept. 24, 1939, in severe status asthmaticus, using as much as 6 cc. of epinephrin per 24 hours with little relief. The use of an oxygen tent seemed to benefit her. During this hospital stay X-ray irradiation to the lungs was given. The patient returned home on Oct. 15, 1939, using 3 to 4 one-fourth cc. epinephrin injections per 24 hours. During the winter of 1939–1940 she was relatively comfortable, remaining in her room most of the time, attended by a nurse; she used epinephrin several times each day. There was no time when she went without epinephrin longer than 12 hours. In those periods when the asthma was worse she also had vasomotor rhinitis and sweats. In April 1940 she began to require more epinephrin and by the end of that month she was again in severe status asthmaticus.

On May 5, 1940 a vaginal smear was taken and found to be of atrophic type. On May 6, 1940, stilbestrol[3] 1.0 mg. daily by mouth was begun. Three days later, on May 9 the asthma was unrelieved and she returned again to the hospital. On May 15 she was much improved and on May 16 all medication except epinephrin was discontinued. One week later she began to get worse and stilbestrol was resumed, 0.5 mg. per day. Because of nausea and vomiting which was probably not due to the amount of the drug, it was discontinued after three days. With but slight interruption the asthma became rapidly more severe and by May 30, in spite of all the accepted means of treatment, oxygen and helium, epinephrin to 16 cc. per day, intravenous glucose and aminophyllin, her condition was desperate. She could no longer sleep, eat, or talk. Her death was considered imminent. Two thousand R.U. per day of estradiol benzoate by intramuscular injection was begun on May 30. On June 3 she required but 12 injections of one-fourth cc. each of epinephrin, and it was certain that she had improved. On June 8, stilbestrol 0.5 mg. daily by mouth, was substituted for estradiol. On June 13, 15, and 16 she used no epinephrin. She left the hospital on June 21. Her progress since May 4, 1940, as measured by 24-hour requirement of epinephrin, and related to pituitary antagonistic therapy, is shown in the figures. She remained in her room during those periods of exacerbation of asthma which occurred when the estrogen was withdrawn because uterine bleeding had appeared, once in July, 1940

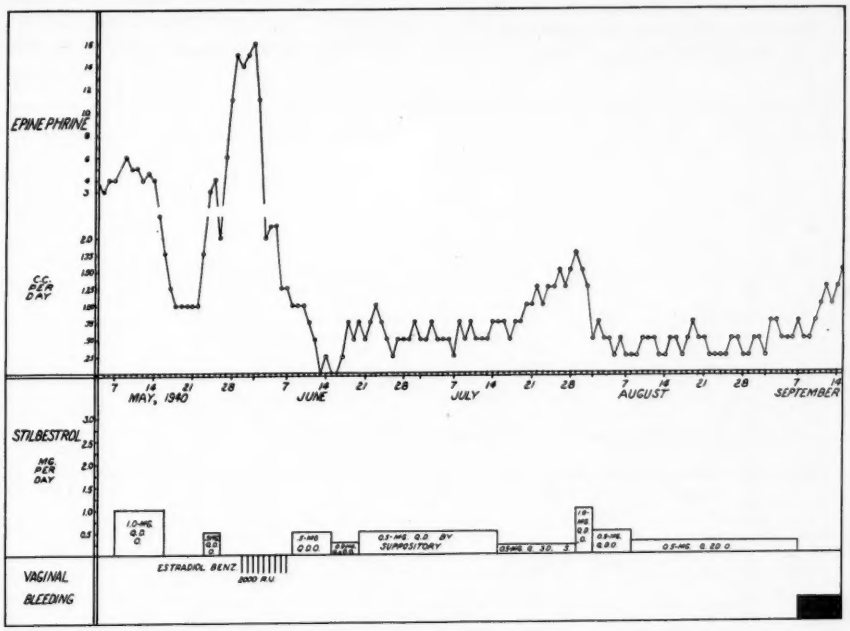

Fig. 1. EPINEPHRIN REQUIREMENT during course of treatment, May to September, 1940.

[2] The histaminase was supplied through the courtesy of the Winthrop Chemical Company, New York City.

[3] The stilbestrol used in this case was furnished by Sharp & Dohme, Baltimore, Md., through Dr. J. L. McCartney, and by Eli Lilly & Co., Indianapolis, Ind., Dr. D. C. Hines. The testosterone propionate was furnished by The Schering Corporation, Bloomfield, N. J., the kindness of Dr. William Stoner.

on low dosage of stilbestrol. At other times the patient was up and about the house until December, 1940. There were three occasions, each one shortly after resumption of estrogen therapy, when she was without need of epinephrin for 48 hours or longer. From Jan. 1 to 10, 1941, she used only 3 injections of one-fourth cc. each of epinephrin; in this period she went 5 successive days with no epinephrin. During the remainder of the time when the asthma was under control she needed one-fourth cc. injections of epinephrin from one to three times in 24 hours, mostly at night. From February 1941 to the time of her death in June she had very few comfortable days.

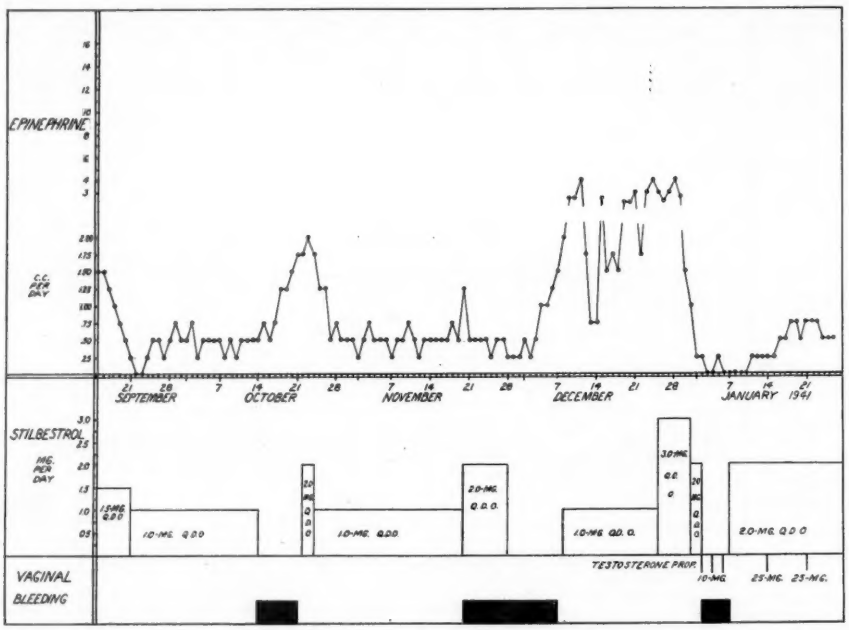

Fig. 2. EPHINEPHRIN REQUIREMENT from September, 1940, to January, 1941.

DISCUSSION OF DATA

Figures 1 to 3 show the relations between the intensity of the asthma, as represented by the amount of epinephrin required per day, and the administration of estrogens and androgen, though the patient's response was more striking than such a simple index can show. It seems apparent that either estrogen or androgen under certain conditions could quite markedly decrease epinephrin requirement. A lag of 3 to 4 days occurred when stilbestrol therapy was discontinued before the asthma became worse; similarly when the drug therapy was resumed some days elapsed before improvement was apparent. Since the severity of the asthma was definitely reduced by estrogen it was hoped that larger doses might produce still greater improvement. In September, 1940 therefore, when stilbestrol had been stopped because of uterine bleeding, it was resumed at a higher dose level. The resultant improvement was little greater than on the lower dose. On Nov. 20, 1940, when bleeding again occurred, instead of stopping stilbestrol the dose was raised from 1 mg. per day to 2 mg. per day in the hope that a dosage larger than the threshold dose might cause a cessation of flow (2). The bleeding continued, and the severity of the asthma remained about the same. No estrogen was given from Nov. 28, 1940 to Dec. 8, 1940, and the patient's condition became much worse. Moreover, on resuming stilbestrol therapy improvement was not as great or as sustained as on previous occasions. The dose was increased on Dec. 25, from 1.0 mg. to 3.0 mg. per day, and relief followed within a few days. With the recurrence of bleeding on Jan. 2, 1941, stilbestrol was stopped and testosterone propionate, 25 mg. every other day, was substituted. It was thought that the androgen would control the asthma equally as well as estrogen by inhibiting pituitary activity, and would allow return of the endometrium to the resting stage, and so permit cessation of bleeding. In the 8 days immediately thereafter, Jan. 3 to 10, but one injection of adrenalin was given, and the patient was more comfortable than at any time since the onset of asthma in

July, 1939. From that time on, however, endocrine therapy gave only slight and fleeting relief, though large doses were used at times. Testosterone propionate, estradiol benzoate and desoxycorticosterone acetate were each tried in large dosage, but they accomplished no more than had stilbestrol. None of these was used for 6 days in April, 1941, and again in May, 1941, and after each of these periods the resumption of stilbestrol was followed by some relief. During May, 1941 the dosage of estrogen was lowered gradually to 0.25 mg. per day. In June, 1941 severe status asthmaticus recurred and the patient died on June 12, 1941. Necropsy performed 5 hours post mortem by Dr. A. M. Young showed the following relevant findings.

Lungs. These were voluminous; the large and small branches of the bronchial tree throughout were plugged with tenacious greyish white viscid exudate. Microscopically, this exudate showed the arrangement characteristic of Curschmann's spirals and Dietrich's plugs. The walls of the bronchial branches and bronchioles were markedly thickened, in great part due to hypertrophy of the muscular coats, and were richly infiltrated by wandering cells with eosinophiles predominating.

Liver. This was of average size and showed no evidence of degenerative change except slight cloudy swelling.

Adrenals. The right adrenal showed at one pole a friable and degenerating adenoma 1½ cm. in diameter. The two adrenals together weighed (exclusive of degenerating adenoma) 16 gm. (normal weight 8–14 gm.). Grossly and microscopically they showed areas of considerable hypertrophy in the cortex.

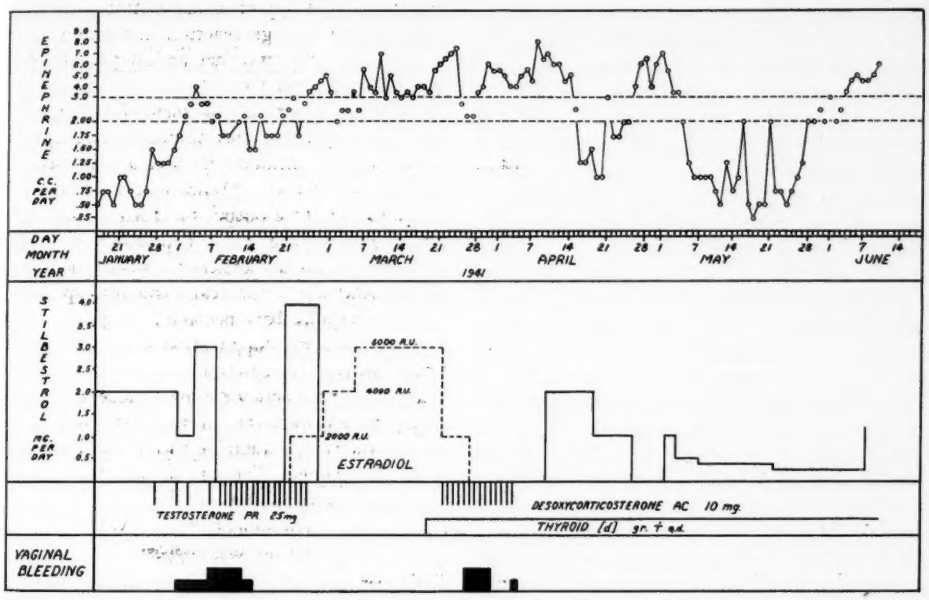

Fig. 3. EPINEPHRIN REQUIREMENT from January, 1941, to June 12, 1941.

Ovaries. These showed marked senile involution.

Uterus. The uterus was small and firm; the endometrium was about 1 mm. in thickness and grossly suggested senile atrophy. Microscopically, however, the appearance of the endometrium was characteristic of an excess estrin-effect with an increase in the size and number of the glands.

Breasts. Grossly these appeared small and atrophic but on microscopic examination there was considerable increase in the amount of acinar tissue over that expected for the age of the patient.

Hypophysis. The gland weighed 0.7 gm. Microscopically, the anterior lobe showed slight replacement fibrosis especially in the region of the stalk. The ratio of eosinophilic, basophilic and chromophobic cells was not abnormal.

Anatomical diagnosis. Chronic and subacute bronchitis and bronchiolitis (marked) with marked mucus plugs in bronchial tree in a case of clinical asthma. Emphysema and fibrosis of the lungs (considerable).

Hypertrophy and hyperplasia of the uterine mucosa and hyperplasia of the acinar epithelium of the breast. Focal hyperplasia adrenal cortex (considerable) involving fascicular zone. Generalized arteriosclerosis (considerable). Hypertrophy of the wall of the left ventricle (slight to moderate).

Pathologic physiology. Hyperthyroidism appearing first at the age of 75 years is of uncommon occurrence. Bronchial asthma as the first manifestation of atopy at the age of 76 years is even more uncommon. The asthma in this patient did not conform to the usual preclimacteric type, in that it was not controlled by environmental change, hyposensitization, and the commonly used drugs. It followed closely the pattern of the later-occurring asthma described by Alexander: "Bronchial asthma, like other atopic conditions, has its onset as a rule in childhood and adolescence. Occasionally it begins in middle life. In such patients, . . . attacks recur with alarming frequency. Within a year asthma may be constant, with episodes of status asthmaticus, wherein violent intractable paroxysms may occur. . . . The beginning of asthmatic attacks in persons over forty years of age should always be viewed with concern" (3). That asthma of this postclimacteric type should follow closely on the heels of hyperthyroidism in an elderly individual, strongly suggested something more than mere chance. It seemed logical to suppose that there might be some etiological relationship between the two disturbances, that they perhaps depended upon a common cause. The possibility of hyperpituitarism as such a common cause was thought of because according to modern concepts (4) hyperpituitarism is a frequent precursor of hyperthyroidism, especially that which develops at the time of the climacteric, of puberty and of pregnancy, and perhaps also after psychic traumata and illnesses.

Changes in the level of pituitary function have been shown to be capable of affecting autonomic balance (5, 6). Hyperpituitarism, then, by reason of its effect upon the autonomic nervous system, might be suspected of altering allergic response. In support of this idea is the fact that changes in gonadal function such as those of puberty, in pregnancy and the climacteric are accompanied by changes in the level of pituitary function, and are at times followed by marked alteration of allergic state.

On the basis of these speculations an hypothesis of the pathologic physiology of this case was set up as follows.

Chronic debilitating illness→Hyperpituitarism→Hypothalamic centers→(Tissues conditioned by inheritance)→Asthma
↙ ↖ (Autonomic imbalance)
Hyperthyroidism→Thyroidectomy

The initial disturbance, fibromyositis, with weight loss, low grade fever, pain and insomnia, interfered with metabolism so as to evoke hyperpituitarism. This in turn stimulated the already goiterous thyroid to the state of hyperthyroidism. Thyroidectomy added further stimulus to the overactive pituitary. Increased output of pituitary hormone affected the autonomic nervous system balance as maintained by the hypothalamic centers so as to lower the threshold of allergic reaction, and asthma appeared in this individual who had an inheritance inclining her to atopic sensitivity.

Rationale of therapy. The central point of therapeutic attack offered by this hypothesis was the hyperpituitarism. Means for such attack are known. Albright (6) showed the inhibitory action of estrogen on the output of prolan. This antagonistic action of estrogen on the pituitary is possessed also by the adrenal cortical hormone, the thyroid hormone, and others. Clinically this principle of endocrine therapy is rapidly becoming of great importance (7–12). Its widest application is in the treatment of the menopausal syndrome.

These were the considerations which led to the use of pituitary antagonistic substances in treatment of the intractable asthma from which this patient suffered. The success during 8 months attending the administration of stilbestrol and various hormones gives support to the working hypothesis on which their use was suggested.

COMMENT

Observation of this patient leaves no doubt in our minds that she was greatly benefited by pituitary-antagonistic therapy, indeed that her life was prolonged by it. For the first 8 months endocrine substances were given in relatively small dosage, and intermittently, and the asthma was kept under control. Shortly after large doses were first used, and especially after the institution of continuous large doses in January, 1941, the asthma became less manageable. Pratt (13) reported a case in which response to the effect of stilbestrol seemed to diminish with long-continued administration. Decrease in efficacy in our case however, was not due to the development of a specific tolerance to stilbestrol, since trial of large doses of testosterone, estradiol and desoxycorticosterone showed that these also were powerless to mitigate the severity of the asthma.

It is possible that the pituitary had been able to develop resistance to the antagonistic effect of these substances when the attempt was made to inhibit its function too drastically and for too long a time. A similar escape from control is frequently seen in cases

of the menopausal syndrome treated with estrogen, and we believe that these cases also do better on intermittent than on continuous treatment. It occurred to us that long-continued inhibition of anterior pituitary function might have resulted in an impairment of adrenal cortical function, and that this in turn might have caused resistance of the pituitary to further inhibition. Blood sodium and potassium levels on March 15, 1941[4] (before desoxycorticosterone had been used) were 373 mg. and 18.5 mg. respectively; these were normal values.

True asthma (not that resulting from pulmonary or cardiac insufficiency) appearing for the first time in persons over 40 years of age is extremely difficult to control. Experience with this case suggests that pituitary antagonistic therapy may be of help in selected instances. Suitable cases for trial of such treatment would seem to be those in which increased pituitary activity has so altered the activity of the autonomic nervous system as to lower the threshold of allergic reaction. Such cases can probably be selected with some assurance when the reaction makes its first appearance after the occurrence of amenorrhea, the climacteric, in association with hyperthyroidism or diabetes or other manifestation of hyperpituitarism. This means, in general, that the patients amenable to such treatment will be of the older age group. In those allergic patients who have conformed to the more usual pattern by demonstrating clear cut specific reactivity and by responding to environmental change and/or hyposensitization, the true atopic factor is the more important element and any neuro-endocrine disturbance which may be present will probably play a minor rôle.

SUMMARY

A case is presented in which bronchial asthma appeared under circumstances which suggested that overactivity of the anterior lobe of the pituitary gland was an important factor in its development.

Pituitary-antagonistic endocrine therapy was used with some success.

The possible significance of these observations in relation to the neuro-endocrine atopic mechanism is discussed.

We wish to acknowledge our indebtedness to Robert R. Sanker for the preparation of the chart.

REFERENCES

1. Thaddea, S.: Allergie und vegetatives system. *Zentralbl. f. inn. Med.* 60: 146. 1939.
2. Zuckerman, S.: The menstrual cycle of the primates. X. *Proc. Roy. Soc., London, s. B.*, 123: 441. 1937.
3. Alexander, H.: Modern medical therapy in general practice. Barr. Williams and Wilkins Co., 1940. p. 973.
4. Marine, D. H.: The pathogenesis and prevention of simple or endemic goiter. *J.A.M.A.* 104: 2334. 1935.
5. Marine, D., and S. Rosen: Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary, and the mechanism involved. *Proc. Soc. Exp. Biol. & Med.* 30: 901. 1933.
6. Albright, F.: Studies on ovarian dysfunction, III. The menopause. *Endocrinology* 20: 24. 1936.
7. Mazer, C., D. R. Maranze and S. L. Israel: Evaluation of the constitutional effects of large doses of estrogenic principle. *J.A.M.A.* 105: 257. 1935.
8. Gessler, C. J., J. A. Halsted and R. P. Stetson: Effect of estrogenic substance on the blood sugar of female diabetics after the menopause. *J. Clin. Investigation* 18: 715. 1939.
9. Cantilo, E.: Successful responses in diabetes mellitus of the menopause produced by the antagonistic action of sex hormones on pituitary activity. *Endocrinology* 28: 20. 1941.
10. Kurzrok, R., and C. P. O'Connell: The inhibition of lactation during the puerperium by testosterone propionate. *Endocrinology* 23: 476. 1938.
11. Papanicolau, G. N., H. S. Ripley and E. Shorr: Suppressive action of testosterone propionate on menstruation and its effect on vaginal smears. *Endocrinology* 24: 339. 1939.
12. Hoet, J. P., and C. Gessler: *Vlaamsch. Geneesk, Tijdschrift* 17: 281. 1937. Cited by Gessler, Halsted and Stetson. Ref. 8.
13. Pratt, J. P.: Stilbestrol. A clinical study in estrogenic therapy. *J. Clinical Endocrinology* 1: 50. 1941.

13224 Shaker Square
Cleveland, Ohio

[4] These determinations were done at the Research Laboratory of Cleveland Clinic through the kindness of Drs. E. P. and Roy McCullagh.

Abstracts of

CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, GEORGE W. THORN, EMMERICH VON HAAM.

ADRENALS

BALASSA, G., AND M. R. GURD.

Action of adrenalin and potential changes in the cat uterus. *J. Pharmacol. & Exper. Therap.* 72: 63. 1941.

In the anestrous cat uterus spontaneous slow rhythmic potentials occur which are slightly increased by a relaxation due to epinephrin, but abolished by a relaxation due to ephedrine. In estrous or late pregnancy uterine contractions, whether spontaneous or drug induced, are accompanied at the beginning of the contraction by short bursts of spike potentials. These are greatly diminished or abolished in early pregnancy when the reaction to epinephrin is reversed. The authors suggest that the conduction of impulses from cell to cell is a characteristic of the estrous uterus and is responsible for the strong and coordinated contractions which occur during this period. In anestrous uteri such conduction does not occur, and during progestational proliferation it is partially suppressed. The uterine contractions are correspondingly feeble during these phases. Conduction may or may not occur during pregnancy, depending on whether the estrogenic or luteal hormone predominates.—*C.P.*

HEATH, F. K., G. F. CAHILL AND D. W. ATCHLEY.

Pheochromocytoma—Correct diagnosis and successful operation. *J.A.M.A.* 117: 1258. 1941.

The case history of a patient with a chromaffin tumor of the adrenal gland is presented. The tumor was removed after diagnosis by the perirenal insufflation of air. The postoperative course was entirely satisfactory.—*C.P.*

THELANDER, H. E., AND M. CHALFFIN.

Neonatal cortical insufficiency (Addison's disease) associated with adreno-genital syndrome. *J. Pediat.* 18: 779. 1941.

A case is reported in a new-born child and the literature reviewed. The symptoms are: *a)* Those due to acute adrenal insufficiency; loss of appetite, diarrhea, vomiting, weakness, anuria, rapid pulse, cyanosis, extreme dehydration, thirst, high temperature at times and perhaps pigmentation. The child does well on salt and poorly without it. *b)* Those due to hypersecretion of androgenic tissue. In females, pseudohermaphroditism generally is present at birth while in males hypergenitalism, pubic hair, gruff voice and advanced bone development appear within a few months. The laboratory findings are those of Addison's disease and high androgen content in the urine. Death occurs in convulsions or coma, in collapse with low temperature or in marasmus. The treatment consists of administration of salt, glucose and cortical extract or D.C.A.—*M.B.G.* (courtesy Clinical Abstracts).

ENDOCRINE GENERAL

BONNYCASTLE, D. D., AND J. K. W. FERGUSON.

The action of pitocin and adrenalin on different segments of the rabbit uterus. *J. Pharmacol. & Exper. Therap.* 72: 90. 1941.

The classification of Gunn and Gunn has failed to clarify the observations or to suggest the functional rôle of adrenergic nerves or of epinephrin in uterine motility. The cervical portion of the uterus is relatively insensitive to pituitary extract, but is very sensitive to epinephrin. It is, thus, deduced that the complex action of epinephrin is anti-expulsive and thus physiologically antagonistic to the action of oxytocin.—*C.P.*

CHRISTIE, U., C. DUNHAM, M. JENSS, AND A. L. DIPPEL.

Development of the center for the cuboid bone in newborn infants. *Am. J. Dis. Child.* 61: 471. 1941.

This is a study of the osseous development of 1,107 newborn—297 white boys, 266 white girls, 268 negro boys and 276 negro girls. Roentgenograms of the infants made within 72 hours of birth showed association of the presence of the center of ossification for the cuboid bone (right side) with race and sex, with certain often used criteria of the maturity of the infant and with the parity and age of the mother.—*M.B.G.*

DENNIS, W.

Effect of pubertas praecox on the age at which onset of walking occurs. *Am. J. Dis. Child.* 61: 951. 1941.

Reports of cases of pubertas praecox have been examined relative to the age at which healthy infants who attained puberty within the first 2 years began to walk. Data were obtained for 25 cases. The range of ages at which walking began in these cases was from 9 to 18 months, with a mean of 13.58. These figures are substantially the same as those for children of normal growth.

Since pubertas praecox is associated with extraordinary bodily changes in the direction of adult size, proportions and ossification, it must be concluded that none of these developments is the final factor the attainment of which marks the onset of walking.—*M.B.G.*

FREED, S. C.

Clinical significance of hormone assays. *J.A.M.A.* 117: 103. 1941.

The studies of hormonal content of urine, blood, and tissues are significant only in relation to clinical history, physical, and other findings of the patient. Definite progress, however, has been made by use of biochemical procedures in determining quantities of certain hormonal substances, especially steroids of ovary, testes, and adrenal cortex. Detailed discussions of the biochemical levels of anterior lobe of pituitary, posterior lobe of pituitary, gonads, adrenal cortex, and pregnancy hormones are given.—*C.P.*

FREED, S. C.

Present status of commercial endocrine preparations. *J.A.M.A.* 117: 1175. 1941.

The commercial hormone preparations are discussed from the standpoint of trade names and potency. The discussion includes estrogens, androgens, progesterone, posterior pituitary preparations, gonadotropins, thyroid, parathyroid and blood Ca raising substances, adrenal cortex, and miscellaneous glandular preparations.—*C.P.*

KERLEY, C. G., AND E. J. LORENZ.

Nutritional obesity in children with private practice. *J. Pediat.* 19: 240. 1941.

The authors report the dietary management of 103 cases of nutritional obesity, in children ranging from 2 to 16. A diet of approximately 1,000 to 1,200 calories with 125 gm. of carbohydrate, 75 gm. of protein and 35 gm. of fat on the average with the addition of Vitamins A, B and D but without glandular therapy resulted in a weight loss of from 3 to 13 lb. in from 3 to 16 weeks.—*M.B.G.*

GONADS

ALBRIEUX, A. S.

Estrogen content of the blood at four-hour intervals. *Proc. Soc. Expter. Biol. & Med.* 47: 380. 1941.

The estrogenic hormone content of the blood of 5 women was determined at 4-hour intervals for one 24-hour period. A significant diurnal rise was noted once, a minor increase in 3 cases and a constant level in one case.—*L. E. Gilson (Courtesy Chem. Abstracts).*

ANONYMOUS.

Oral androgenic therapy. Current comment. *J.A.M.A.* 117: 622. 1941.

Methyl testosterone is compared with testosterone. Because of itsrelatively recent introduction, the only worthwhile indication is the application in treatment of eunuchoidism or castration. Other indications must await further investigation.—*C.P.*

BURLINGAME, C. C., AND MARJORIE B. PATTERSON.

Estrogen therapy in the psychoses. *J. Nerv. & Ment. Dis.* 94: 265. 1941.

Estrogen therapy has been employed as part of the treatment program in 139 psychoses. Estradiol benzoate or estrone was employed. The dosage was controlled by vaginal smears, 2,000 to 3,000 R.U. daily being generally given, intramuscularly, for 30 to 40 days. The most favorable results were obtained in the depressions of the climacterium. Fifty-nine per cent of 63 involutional psychoses and 52% of 27 manic depressive psychoses in the depressed phase showed definite improvement, and in some instances recovery, coincident with therapy. The miscellaneous psychoses and the schizophrenia of the involutional period showed no fundamental change associated with this form of therapy.—*R.G.H.*

BURN, J. H., AND E. R. WITHELL.

A principle in raspberry leaves which relaxes uterine muscle. *Lancet* 1: 3. 1941.

Experiments are reported showing that dried raspberry leaves contain a principle readily extracted with water which relaxes the smooth muscle of the uterus and intestine when this is in tone. The action is exerted in the body of the cat and also when the muscle is suspended in a bath. The relaxation produced in the body increases with successive doses. The same principle or another causes contraction of the uterus of the rabbit in situ, and also of the isolated uterus of the cat, the rabbit and the guinea pig when these are not in tone. The principle causing relaxation is probably the basis of the traditional use of raspberry tea for making activity in the uterus less painful. A drug which relaxes uterine muscle should be valuable in relieving painful menstruation when this is due to spasmodic contraction of the uterus. The dosage recommended by herbalists is 10 to 20 oz. of a 5% infusion of the dried leaves in hot water. This corresponds to 15 to 30 gm. of leaf, and judging from the observations in mice, should be entirely non-toxic when taken by mouth.—*Courtesy Clin. Abstracts.*

CURRIER, F. P., C. H. FRANTZ AND R. VANDER MEER.

Reduction of growth rate in gigantism treated with testosterone propionate. *J.A.M.A.* 117: 515. 1941.

In this case report the male sex hormone has been used as a physiological brake on the growth-promoting hormone of the anterior pituitary. Treatment over a 2-year period resulted in a decrease of growth rate when compared to the preceding 2 years.—*C.P.*

DE TAKATS, G., AND L. S. HELFRICH.

Sterility of the male after sympathectomies. *J.A.M.A.* 117: 20. 1941.

After extensive removal of the lumbar and thoracic sympathetic chains a patient still had normal spermatozoa,

although 4 months had elpased since the last operation. This finding contradicts the opinion that such sympathectomies produce sterility in the male.—*C.P.*

EIDELSBERG, J., AND I. MADOFF.

Effectiveness of methyl testosterone administered orally. *Am. J. M. Sc.* 202: 83. 1941.

Methyl testosterone, administered orally, 100 to 150 mg. per day, was effective in inducing testosterone effects in several different types of patients, all with hypogonadism. Its continued use maintained the effects of testosterone administration. In general, it appears that the earlier changes may be brought about more rapidly by injections of testosterone propionate. All the observations originally made following injections of testosterone propionate in such cases were found in this group with oral administration. Toxic or unusual responses were minimal. None of the patients complained of gastric distress or upsets. The time of dosage or its relation to meals apparently made little, or no difference. The extremes in variation of response may be due to individual case variations or require further study in dose. Methyl testosterone orally appears to be a good, safe, substitutive form of male sex hormone therapy. *Courtesy Clin. Abstracts.*

EIDELSBERG, J., AND E. A. ORNSTEIN.

Observations on the implantation of testosterone pellets. *J.A.M.A.* 117: 1067. 1941.

The authors present 9 case histories all of which indicate that the implantation of pure testosterone tablets offers a means of prolonged androgen therapy. In a series of 130 implants no accident or complication occurred. They now use a bevelled trocar for the implants.—*C.P.*

FRANK, R. T., AND R. L. BERMAN.

A twenty-four-hour pregnancy test. *Am. J. Obst. & Gynec.* 42: 492. 1941.

An inexpensive pregnancy test requiring only 24 hours (and possibly only 8 hours) is described as being equal in accuracy to the A-Z and Friedman tests. Two female white rats (weight 50 gm.) are each given subcutaneously 5 cc. of fresh first morning urine at 10 A.M. and 4 P.M. and autopsied at 9 A.M. the following day. Ovarian readings are made microscopically and with 10 loupe enlargement by transmitted light. Positive tests have been obtained in 8 hours by the use of 2 four-hourly injections of 5 cc. of urine.—*E.C.H.*

GRAUER, R. C., C. F. BEALL, AND G. R. WILSON.

Endometrial response to diethylstilbestrol in radium-induced menopause. *Am. J. Path.* 17: 87. 1941.

The endometrial and vaginal response to stilbestrol in 10 radium-treated cases was delayed, and the dose required was greater, as compared to cases of physiological menopause. The stilbestrol produced a proliferative endometrium and stroma which duplicated the appearance of the endometrium before radium was inserted. These studies confirmed the belief that cases in which an artificial menopause has been produced by radium are more refractory to stilbestrol than cases of surgical sterilization or those associated with normal physiological processes. In the physiological menopausal cases the endometrium remains intact even though it becomes atrophic. In the radium-treated cases we are dealing with the dual effects on the endometrium of the physiological regression incidental to menopause, age, plus the destructive effects of radium.—*Courtesy Clin. Abstracts.*

GREENHILL, J. P., AND S. C. FREED.

The electrolyte therapy of premenstrual distress. *J.A.M.A.* 117: 504. 1941.

The symptoms of premenstrual distress and tension are ascribed to the accumulation of extracellular water and Na retention, which probably results from cyclic ovarian activity. In the brain this may result in headache; in the gastro-intestinal tract distension, nausea, etc. may occur; while in the labia the swelling may cause pruritis. Various methods of treatment are described, but the authors advocate ammonium chloride 3 gm. daily beginning 10 to 12 days before the expected menstrual period.—*C.P.*

HECKEL, N. J., AND C. R. STEINMETZ.

The effect of female sex hormone on the function of the human testis. *J. Urol.* 46: 319. 1941.

An estrogen (α-estradiol benzoate) produced sterility in man. It caused a temporary hypertrophy of the male breasts and enlargement of the nipples. Partial impotence developed.—*Authors' summary.*

KLEIN, M. D., AND M. SAROKA.

Studies in viability of human spermatozoa. *Am. J. Obst. & Gynec.* 42: 497. 1941.

A simple method of determining sperm viability, which utilizes methylene blue as an indicator of the absorption of free O_2 is described. The method employed is the following: 1 cc. of spermatic fluid and 1/10 cc. of methylene blue solution are placed in each of 2 ordinary Wassermann tubes and are mixed thoroughly. Each tube is layered with a little heated vaseline. One tube is placed in incubator at 37° C. and the other is kept at room temperature (20° C.). Readings are taken every 15 minutes. Decolorization of the methylene blue results from the utilization of available oxygen by viable sperms. It is preseumed that significant relationship exists between decolorization time and sperm viability.—*E.C.H.*

LEWIS, A. A., AND C. W. TURNER.

Effect of stilbestrol on the mammary gland. *Proc. Amer. Soc. Animal Prod.* 33. 63. 1940.

Stilbestrol was reported to stimulate the growth of mammary ducts, and some lobule-alveolar tissue, but differed from estrogen in having ability in addition to stimulate milk secretion in virgin or dry animals. It did not consistently stimulate glands already in lactation.—*C. C. White (Courtesy Biol. Abstracts).*